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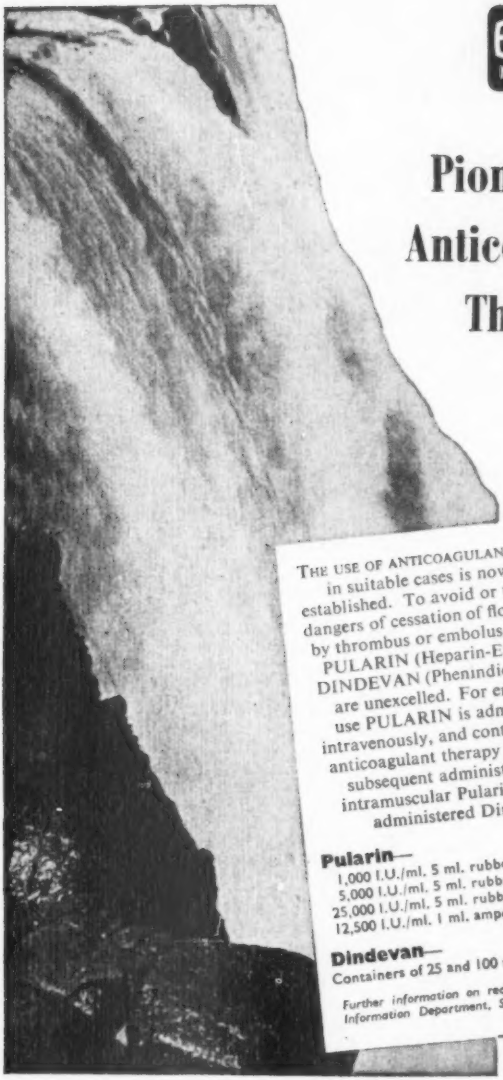

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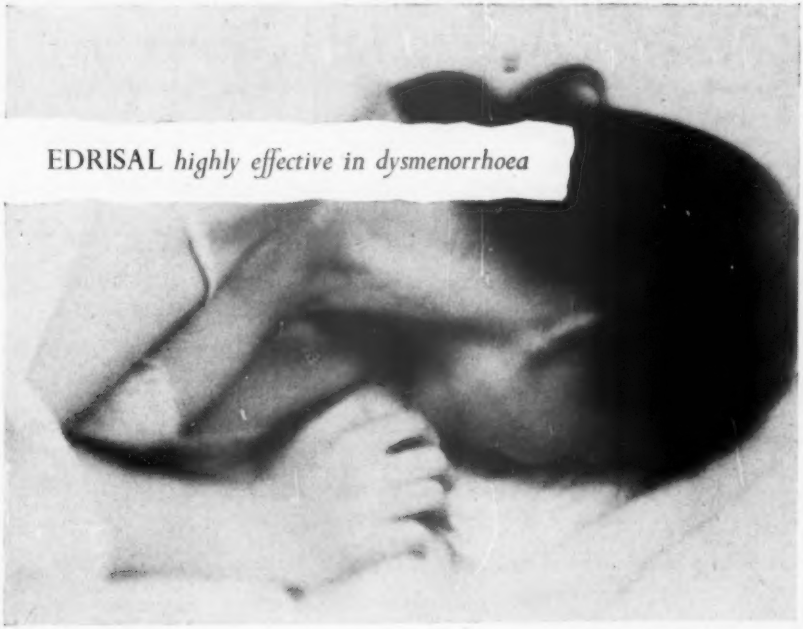

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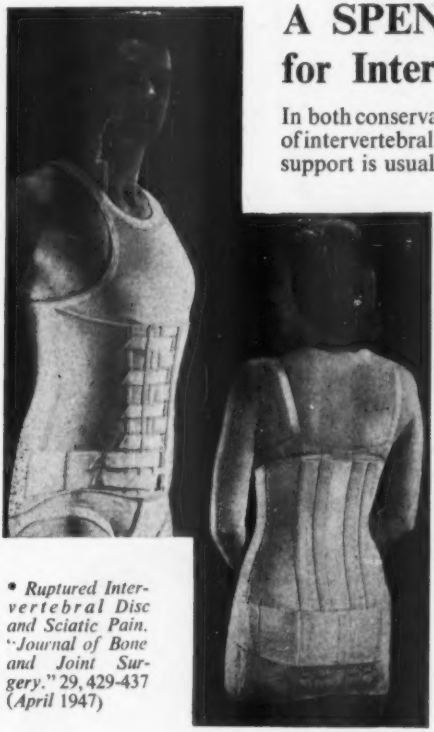

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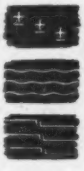

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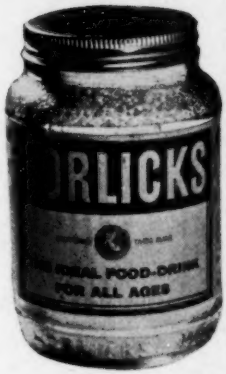

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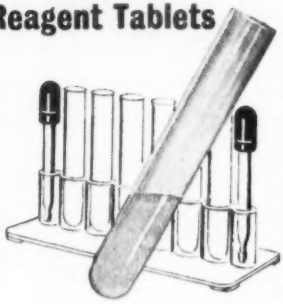


for the detection of PROTEIN

Technique

BEFORE TESTING, FILTER URINE IF NOT CLEAR

1 Pour 1 inch (4 ml. of urine) into a 'CLINITEST' Test Tube.
2 Add 1 tablet.
3 When completely dissolved shake test tube gently to disperse small bubbles, and liquid should be yellowish.

NEGATIVE: Clear solution.

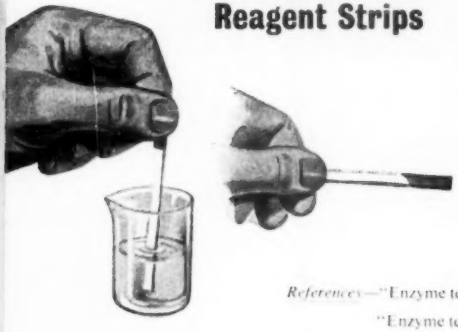
POSITIVE: Cloudiness or precipitate according to the amount of protein.

IMPORTANT:

Sometimes urine will be very alkaline and after dissolving 1 tablet the solution will be blue or green. Additional tablets must then be dissolved one at a time until the last trace of green disappears. Shake tube gently as above and read result.

THIS STEP AVOIDS THE RISK OF MISSING PROTEINURIA IN VERY ALKALINE SPECIMENS

*CLINISTIX Reagent Strips



for the detection of *true* GLUCOSE

Technique

DIP TEST END OF 'CLINISTIX' IN URINE AND REMOVE

NEGATIVE: No blue colour develops.

POSITIVE: Moistened end turns blue, usually within one minute.

IMPORTANT:

Due to the effect on enzyme paper tests of variable factors in urine, this method should not be relied upon for quantitation.

References—"Enzyme tests for the detection of glucose", Brit. med. J., 2, 586 (Sept 8th, 1956)

"Enzyme test for glycosuria", Brit. med. J., 2, 588 (Sept. 8th, 1956)

*CLINITEST Reagent Tablets

for the detection *and* estimation of SUGAR

Technique

1 Place 5 drops of urine in test tube
Rinse dropper and add 10 drops of water.
2 Drop in 1 'CLINITEST' Tablet and watch reaction.
3 15 seconds after boiling stops, shake tube gently and compare with 'CLINITEST' colour scale.

NEGATIVE: Solution in test tube is blue.

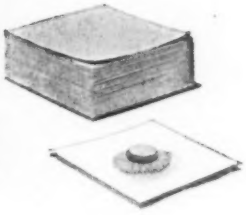
POSITIVE: Any colour other than blue.
Compare with 'CLINITEST' colour scale

All the above colours are for illustration only. Do not use for actual tests. Write to Ames Company for standardised colour scales and full information.

*TRADE MARKS

ABLE ROUTINE URINE TESTS

*OCCULTEST
Reagent Tablets



for the detection of BLOOD

Technique

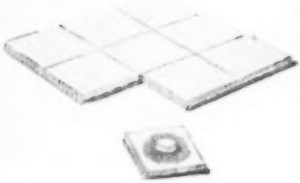
1 Place 1 drop of well-mixed *uncentrifuged* urine in centre of filter paper provided.
2 Put 1 'OCCULTEST' tablet in centre of moist area.
3 Place 2 drops of water on tablet.

NEGATIVE: No blue colour *on the paper* at the end of 2 minutes.

POSITIVE: A diffuse area of blue colour appears *on the paper* surrounding the tablet within 2 minutes after adding the water.

SENSITIVITY: The test will detect approximately 50 R.B.C's per c.mm. when read at 2 minutes.

*ICTOTEST
Reagent Tablets



for the detection of BILIRUBIN

Technique

1 Place 5 drops of urine on one square of test mat supplied.
2 Put 'ICTOTEST' Tablet in the centre of the moist area.
3 Place 2 drops of water on to the tablet.

NEGATIVE: Mat shows no colour within 30 seconds or may appear pink or red.

POSITIVE: Mat around tablet turns bluish-purple. Amount of bilirubin is proportional to speed and intensity of colour.

*ACETEST
Reagent Tablets

for the detection of ACETONE & DIACETIC ACID

Technique

1 Place 'ACETEST' tablet on a clean white surface.
2 Put 1 drop of urine on the tablet.
3 Take reading at 30 seconds. Compare tablet to 'ACETEST' colour scale.

NEGATIVE: Tablet remains white or turns creamy in colour.

POSITIVE: A mauve colour appears within 30 seconds which should be compared with 'ACETEST' colour scale.

IMPORTANT:
A 'moderate' or 'strongly positive' result can indicate a severe degree of ketosis.

For the Doctor

For the Patient too

Available under the N.H.S. on Form E.C.10.

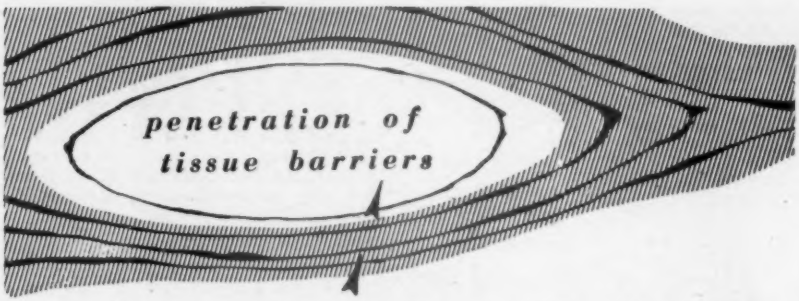
Diagnostic Reagents for Routine Urine Testing by

AMES COMPANY (LONDON) **LIMITED**

NUFFIELD HOUSE · PICCADILLY · LONDON W1

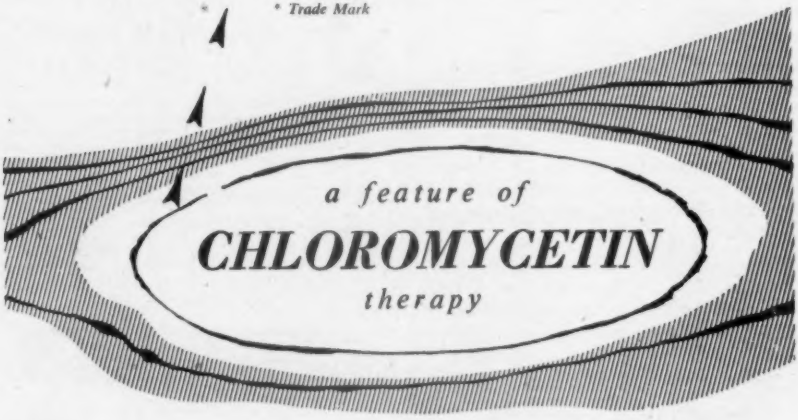
Sole distributors for the United Kingdom and Eire

DON S. MOMAND LIMITED



Chloromycetin* is unequalled amongst antibiotics in its ability to diffuse readily throughout the body and to penetrate tissue barriers, including the blood, brain, placental and ocular barriers. Adequate therapeutic concentrations can be achieved in relatively inaccessible parts of the body *by oral administration*. Effective blood levels are quickly obtained, and blood levels can be adjusted to meet any grade of infection. Because of the relative completeness of absorption, gastro-intestinal upset is unlikely to occur.

* *Trade Mark*



Parke, Davis & COMPANY LIMITED. (*Inc. U.S.A.*) HOUNSLOW, MIDDLESEX. Tel. Hounslow 2361.

437

FOR FIRM SUPPORT

The *Remploy* tripod walking-stick

This walking-stick, especially designed for its job by Remploy, gives remarkable confidence and security to its user by its firm 3-point contact with the ground.

The stick stands independently by chair or bed—ready for use, and easily reached, whenever it is wanted.

It is made in a light alloy in three sizes (adult's, intermediate and child's) and the adjustable handle has a felt padded grip covered in soft leather.

The tripod stick has already proved itself as an invaluable aid to many aged and disabled persons, who would otherwise be immobilised.

We strongly recommend you to keep this appliance always in mind for those who are under your treatment and care. Samples will be gladly sent to anyone with such responsibilities, for examination and trial.

REMPLOY LIMITED
Engineering and Hospital Sales Dept.,
Oxgate Lane, Cricklewood, N.W.2.
Telephone: GLAdstone 8020

For 40 years
"EUPINAL"

has been used successfully in the treatment of ASTHMA and CHRONIC BRONCHITIS and may be prescribed on N.H.S. Form E.C. 10

"Eupinal" contains Iodine and Caffeine combined in a most elegant and effective form.

In chronic Bronchitis "Eupinal" softens the tough accumulated mucus in the bronchial tubes and allows it to be more readily expectorated. In Asthma it possesses a more markedly soothing effect, lessening the frequency of attacks and reducing their severity and duration, and relieving breathlessness.

"Eupinal" contains no poison and is safe in use.

A PRODUCT OF
Cuxson, Gerrard & Co. Ltd.
OLDBURY BIRMINGHAM
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HASTINGS and THANET —

3 3/4% *Important New* "TERM SHARES" FOR SAVERS!

One of the leading Societies, with great Reserves and liquid strength, now offers discriminating savers a NEW "TERM SHARE" PLAN for sums from £250 to £2,000, withdrawable at six months' notice, Interest, 3¾% net, being equivalent to £6.10.5d% to anyone liable to Income Tax at the Standard Rate.

REGULAR SAVERS can earn a net 3½% net for Fully-Paid Shares £1 to £5,000 Income Tax paid by the Society 4%

Without obligation, call or write for our booklet, "Profitable Investment"

***Hastings and Thanet* BUILDING SOCIETY**

Established over 100 years
Assets £20,000,000 *Reserve Strength £1,000,000*
Head Offices: **HASTINGS** *and* **RAMSGATE**
LONDON: 99 BAKER STREET, W.1
Branches and Agencies throughout the Country

When prescribing infra-red or ultra-violet rays for self-treatment . . .

. . . remember these advantages

# of PHILIPS Health Lamps

(Made in Holland)

INFRAPHIL—*MODEL "B"*

This is a simply constructed and lightweight lamp that helps, quickly and comfortably, to relieve many ailments of a rheumatic nature. The patient can, after medical advice, give himself home treatment in a standing, sitting or lying position and in any room where there is an electric point. The lamp is obtainable only on production of a signed medical certificate. **Price £3 . 3 . 0.**

INFRAPHIL—*MODEL "A"*

Basically, this is the same lamp as the one above. It has, however, been given a streamlined, robust stand, the base of which enables the lamp to be more easily fixed to a wall and the rays directed downwards. INFRAPHIL is particularly suitable for sportsmen and athletes, who will use it as an aid to massage and for the relief of sprains, bruises and muscular fatigue. Obtainable on medical certificate only. **Price £4 . 4 . 0.**

Ultra-Violet **SUNLAMP**

Compact and attractive in appearance, this Philips ultra-violet lamp has the double advantage of portability and manoeuvrability. It is simple and safe for your patients to use, under Medical Guidance, in the comfort of their own home. Goggles are, of course, essential and these are provided with the lamp. Again, a signed medical certificate is necessary for purchase. **Price £5.17.6.**

We shall be glad to supply further details of any of these lamps. Please address your enquiries to:

PHILIPS ELECTRICAL LIMITED

Electrical Appliances Division · Century House · Shaftesbury Avenue · London · W.C.2

INF10588

SEA PEARLS

-the new small fish oil capsules

Children especially will find SEA PEARLS easier to swallow because they are so small. The capsules are seamless and ensure the fish-oil content is kept in good condition over a long period. Only finest blended fish liver oils are used—to provide a well balanced vitamin content in a remarkably small capsule. Supply is in tins of 100 which release one capsule at a time. Price 5/- per 100.

EACH CAPSULE PROVIDES
4,500 I. UNITS VITAMIN A
AND 450 I. UNITS VITAMIN D

Manufactured by A/S APOTHEKERNES LABORATORIUM, SKÖYEN PR. OSLO, NORWAY.

Sole Distributors for Great Britain :

MAYBORN PRODUCTS LTD., PHARMACEUTICAL DIVISION,
DYLON WORKS, SYDENHAM, LONDON, S.E.26.

Acnil

For the treatment of Acne Vulgaris—

Acnil combines the therapeutic qualities of Resorcinol, Cetrimide and Precipitated Sulphur in a masking cream base. The base is flesh-tinted to conceal the acne spots during treatment and women patients can apply face powder over Acnil without detriment to its curative action.

	FORMULA
Acnil	Resorcinol 4% Precipitated Sulphur 3% Cetrimide 4%
Basic N.H.S. price 1 oz. pack 2 3d.	in a masking base.

The word Acnil is a regd. trade mark of

Genatosan Ltd., Loughborough, Leics.

Catarrh, blocked sinuses, rhinitis—these are the complaints that will cause congestion in your waiting room this winter. Yet, with ARGOTONE Ready Spray you can clear congestion in patient *and* waiting room—speedily, safely, surely. Combining the acknowledged vaso-constrictor, ephedrine hydrochloride, and the highly efficient antiseptic, silver vitellin, in aqueous isotonic solution, ARGOTONE gives rapid prolonged nasal patency without rebound congestion. ARGOTONE is tasteless, odourless, and does not sting or burn. When used in the handy polythene squeeze bottle, "Ready-Spray", ARGOTONE can be carried in pocket or handbag to clear congestion whenever it's needed.

ARGOTONE

"Ready-Spray"

the nasal spray that keeps catarrh at bay

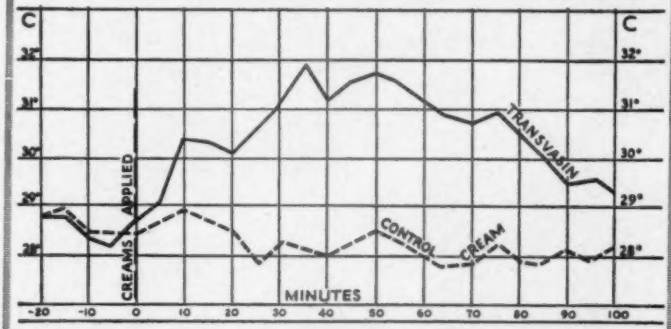
ARGOTONE "Ready-Spray" Basic N.H.S. price 2s. 10d. containing 15cc. Prescribable on Form E.C.10.

ARGOTONE is also available as Nasal Drops in 20cc. bottle complete with dropper, and in 4oz. dispensing pack.

Literature and samples gladly on request.

RONA LABORATORIES LTD. 12-13 MOLYNEUX ST. LONDON W.1

An experiment to show the effect of Transvasin on skin temperature



The graph above is of an experiment to measure the effect of Transvasin on skin temperature on a subject. The solid line plots the skin temperature before and at intervals after a single application of one inch of cream (0.924 grams) from a tube of Transvasin. The broken line gives similar information with regard to the application of a plain vanishing cream used as a control. Skin temperatures were measured with an electro-thermo couple every five minutes for two hours.

IT IS generally agreed that cases of soft-tissue rheumatism and of many types of arthritis benefit by hyperaemia of the affected tissues. Transvasin, which contains two quick-acting esters of nicotinic acid, induces such a deep and prolonged hyperaemia at the same time as it produces superficial erythema.

In addition to the esters of nicotinic acid, Transvasin contains the fat- and water-soluble esters of salicylic and p-aminobenzoic acids. Both these well-tried analgesic drugs are readily conveyed through the skin in therapeutic quantities and enable an effective concentration to be built up where they are needed.

Transvasin is now being widely prescribed, with successful clinical results. Since a very small quantity is sufficient for each application, the cost of treatment is extremely low.

COMPOSITION

Salicylic acid tetrahydrofur-furyl-ester	14%
Nicotinic acid ethyl-ester	2%
Nicotinic acid n-hexyl-ester	2%
p-Aminobenzoic acid ethylester	2%
Water-miscible base ad ...	100%

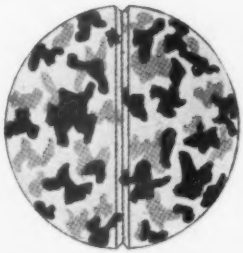
Transvasin is available in 1 oz. tubes, basic N.H.S. price of 2/6 + Purchase Tax, and is not advertised to the public. Samples and literature will be gladly sent on application.

Transvasin

LLOYD-HAMOL LTD., 11 WATERLOO PLACE, LONDON, S.W.1. WHitehall 8654/5/6

'Transvasin' is a registered trade mark of Lloyd-Hamol Limited

Belladenal



retard

sustained-action tablets

(Each tablet contains: 0.25 mg. L-alkaloids of belladonna and 50 mg. phenobarbitone)

Gradual liberation of the active principles provides sustained action for about 10 hours

One tablet morning and evening ensures round-the-clock action

Samples will be gladly supplied upon request

SANDOZ

SANDOZ PRODUCTS LIMITED, 134 WIGMORE STREET, LONDON, W.1

ASPECTS OF A CONDITION

Bitten finger nails . . . mute witnesses to the conflict within the mind. Covatin provides daytime sedation without hypnosis. Covatin is to be preferred to phenobarbitone for it does not interfere with the alertness of the patient. Covatin is not habit-forming and has no side-effects. Covatin is available as 50 mg. sugar-coated tablets in bottles of 50 and 500.

Covatin

TRADE MARK

Formula: p-butylthiodiphenyl-methyl-2-dimethylaminoethyl sulphide hydrochloride

WARNER

WILLIAM R. WARNER & CO. LTD · POWER ROAD · LONDON · W.4

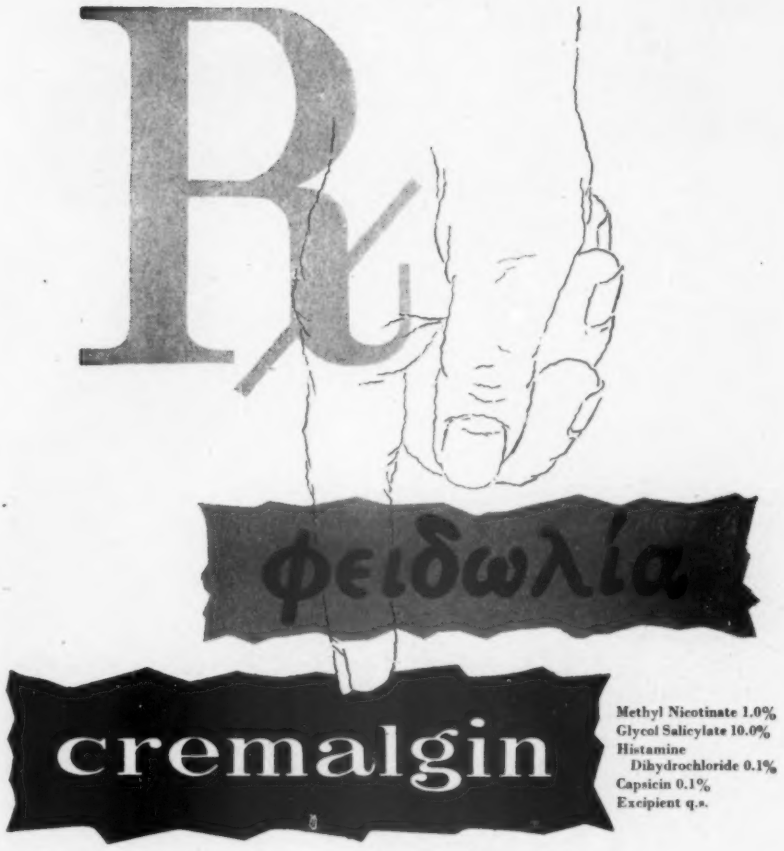
COV 826/11

Would he have got better without you?

DESPITE more medication than ever before, the less dramatic diseases advance in all sections of society. Is this due to a continuous deterioration in the environment or is it perhaps because medication is often haphazard and sometimes even harmful? The nature of peptic ulcer is obscure but it is probable that a substantial proportion of all people are constitutionally disposed to ulcers under certain conditions. One of the factors may be that their acid-secretory mechanism is over-efficient, and, given the right stimuli, produces a degree of acidity which in some way leads to the formation of an ulcer. The initial stimulus may be complex but in making himself comfortable the patient will almost inevitably reduce the acidity below normal. He will thus provide a new stimulus to secretion, and, by following such a regimen over a period, so exaggerate his constitutional condition that even when the original stimulus is removed he continues to over-secrete acid. Thus a temporary disorder becomes a permanent disability. The patient becomes another chronic ulcer case. Yet without medication he would probably have recovered completely.

Although some of this argument may be conjectural, it is almost always wrong to reduce acidity below normal. The one safe therapy in the present state of knowledge is that which restores the acid level to within the normal tolerance and at the same time inactivates the pepsin. The only satisfactory compound known to us which does this is Bismuth Aluminate $Bi_2(Al_2O_4)_3 . 10H_2O$, now available to the medical profession under the trade name Bislumina. This preparation has been placed in Category 3 by The Ministry of Health Standing Joint Committee and is prescribable on Form E.C.10.

RESEARCH DEPARTMENT · MINING & CHEMICAL PRODUCTS LTD · 86 STRAND, LONDON, W C 2



Cremalgin has always meant Economy without detriment to the treatment of N.H.S. patients.

Indications: **Rheumatism, Fibrositis, Sciatica, Lumbago, Muscular Pain, and associated conditions.**

Packed in 1 oz. dispensing tubes at 21/- per doz. plus 30% p.t. and in 16 oz. dispensing jars at 19/6d. per unit plus 30% p.t.

WEST PHARMACEUTICAL CO. LTD. VICTORIA STREET S.W.1. Tel: TAT 2580

The indication for Daprisal is

'Daprisal' is potent enough to be effective when ordinary analgesics fail. Yet 'Daprisal' is safe enough for routine use in conditions such as simple headache. Typical indications are:

herpes zoster · **post-influenzal malaise**

migraine · **rheumatoid arthritis**

headache · **trauma**

sinusitis headache · **surgical pain**

'Daprisal' is both safe and potent. It is the analgesic of choice in all but the mildest or the most agonizing pain.

Daprisal defeats pain

Smith Kline & French, Coldharbour Lane, London SE5

DS:PA17

Furadantin★

BRAND OF NITROFURANTOIN

for urinary tract infections

Duncan

Furadantin is an antibacterial compound for the oral treatment of urinary tract infections only. Therapeutic concentrations up to 400 mcg./ml. appear in the urine but blood and tissue concentrations are very small. The drug is effective against most organisms found in the urinary tract, including *Proteus* and *Aerobacter*, and some strains of *Pseudomonas*.

Advantages

- Oral administration
- Broad antibacterial spectrum
- Action confined to urinary tract
- Only minor side-effects

Furadantin (brand of nitrofurantoin) is available as tablets of 50 mg. in bottles of 25 or 250.

Further information on the use of Furadantin, or Diagnostic Tablets for bacterial sensitivity tests, will be sent on request.

DUNCAN, FLOCKHART & CO., LTD.

16, Wheatfield Road, EDINBURGH, 11

4, Carlos Place, LONDON, W.1

★ *Furadantin is manufactured by a registered user of the trade mark under licence from the Norwich Pharmacal Company (Eaton Laboratories Division).*

DALZOBAND MEDICATED BANDAGES

An Unna's type bandage, always moist, always ready to use. There are five varieties, all conforming to the specifications of such bandages in the Drug Tariff. The medicaments are: zinc paste: zinc paste and ichthammol 2%: zinc paste with urethane 2% and ichthammol 2%: zinc paste with urethane 2% and calamine 5.75%: zinc paste with coal tar 3%.

AVAILABLE ON E.C.10

The Doctor's Cabinet contains 180 waterproof dressings plus a one-yard spool of Dalmas strapping

DALMAS

DALMAS LTD., LEICESTER & LONDON *Established 1823*

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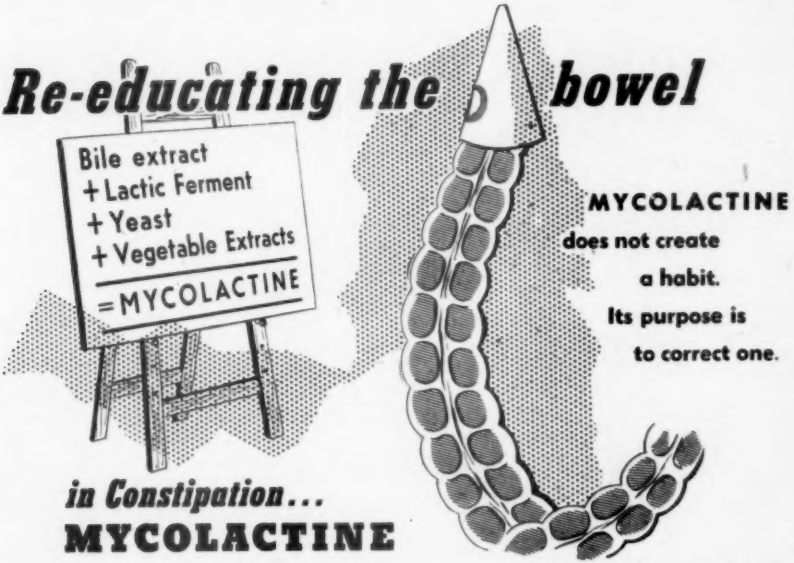
Re-educating the bowel



MYCOLACTINE
does not create a habit. Its purpose is to correct one.

in Constipation...
MYCOLACTINE

The ANGLO-FRENCH DRUG CO. LTD., 11-12 Guilford Street, London W.C.1

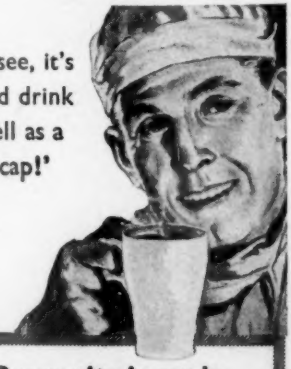
THE SAFEST AND BEST PREPARATION OF OPIUM

Nepenthe contains all the constituents of opium and has been prescribed for over 100 years. It has been found by generations of Practitioners to be the best preparation of Opium as it does not cause the unpleasant after-effects usually attributed to opiates. It can be given over a considerable period and the effect remains invariably constant.

Packed in 2-oz., 4-oz., 8-oz. and 16-oz. bottles and for injection in ½-oz. rubber-capped bottles, sterile, ready for use.

NEPENTHE
Regd.
FERRIS & CO LTD
BRISTOL
Tel. 21381 Grams. "Ferris" Bristol

'You see, it's a food drink as well as a nightcap!'



Bourn-vita is made from malt, milk, sugar, cocoa and eggs
sleep sweeter
BOURN-VITA
made by CADBURYS

in hypertension

smooth predictable control now possible ORALLY

ORAL CONVENIENCE WITH PARENTERAL RELIABILITY

Smooth control of hypertension with *oral* medication is possible *only* if the drug used is readily and dependably absorbed.

'INVERSINE' alone of all available ganglionic blocking agents is *completely absorbed when given orally.* 'INVERSINE' is a secondary amine, *not* a quaternary ammonium compound. The effect of any given dosage on any one patient is entirely predictable—hitherto impossible with oral hexamethonium or pentolinium compounds.

'INVERSINE' *offers these advantages :— Minimal fluctuation of blood pressure • Reproducible clinical response • Gradual onset and long duration of action • Small dosage • Effective in cases resistant to hexamethonium • Tolerance infrequently encountered • Parenteral administration unnecessary.*

'Inversine'

TRADE MARK

Mecamylamine Hydrochloride TABLETS

'Inversine' (Mecamylamine Hydrochloride) 10 mg. quarter-scored tablets are supplied in bottles of 100.

MSD

MERCK SHARP & DOHME LIMITED, HODDESDON, HERTS

Literature and professional package gladly sent on request.

The ONLY CHEESE containing Lactobacilli in ACTIVE FORM

It is true that no other cheese is like St. Ivel, not only is this because no other cheese has the delicious cheddar flavour and creamy texture, but also because it is the only cheese containing Lactobacilli in active form.

The reason for this is that instead of using an ordinary cheese starter of lactic strepto-cocci, a culture of specially selected strains of Lactobacilli is used. The cultures are maintained by professional bacteriologists with specialised knowledge of bacterial selection and genetics.

Great importance is attached to this aspect and to the nutritional requirements of the Lactobacilli so as to maintain the activity of the culture in the cheese after manufacture, and to ensure maximum therapeutic value.

Special hospital packs available.

Communications should be addressed to The Director, Central Laboratory, Aplin & Barrett Ltd., Yeovil, Somerset.

FRESH UP FROM SOMERSET

"I'm actually enjoying this soft diet, doctor!"

Few patients like the idea of a soft diet. But they'll cheer up and take an interest when you tell them about Heinz Strained Foods.

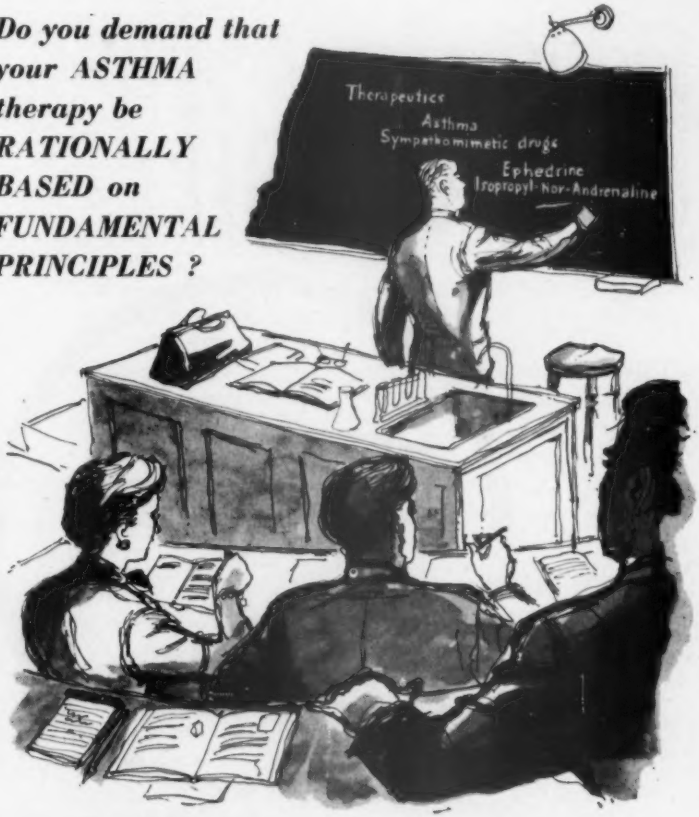
These ready-to-serve, appetizing foods contain no spices or strong-flavoured seasonings. They are just freshly gathered fruits and vegetables, and choice meats, cooked to retain the maximum flavour and nutritional values. The scientific care that goes into them makes them better than most home-prepared diets. The exact nutritional values of each variety of Heinz Strained Foods are set out in a special booklet. Please write for a free copy.

There are 19 varieties from which soft diets can be planned, including soups, meat broths, vegetables, fruits and cereal. A full list is given in the special booklet.

For hospital use, Heinz Strained Foods are obtainable in 15½-oz. cans from the usual suppliers, or direct from H. J. Heinz Company Ltd., Harlesden, London N.W.10.

57 HEINZ
Strained Foods
make a soft diet interesting

Do you demand that your ASTHMA therapy be RATIONALLY BASED on FUNDAMENTAL PRINCIPLES ?



ISO-BRONCHISAN was first produced in 1953 and its modus operandi in bronchial asthma demonstrates that, as in education so in therapy, the best is rationally based on fundamental principles. The outer layer of the Iso-Bronchisan tablet, containing Isoprenaline, is quickly absorbed from beneath the tongue affording rapid relief from bronchospasm. The core, containing ephedrine and theophylline, is then swallowed and slowly absorbed with a resulting sustained bronchodilation, thus combining well established immediate and long acting bronchodilators in one tablet. **Prescribable on E.C.10.**

Each Iso-Bronchisan tablet contains Isopropyl-Nor-Adrenaline (Isoprenaline) sulphate .. gr. ¼
Ephedrine hydrochlor. .. .. gr. ⅜
Theophylline .. .. gr. 2
(Special tablets available for children.)

Samples and literature available on request from
SILTEN LIMITED · SILTEN HOUSE · HATFIELD · HERTS

INTRODUCING

sterisil

TRADE MARK

Active against all the common pathogenic organisms of the vagina including Trichomonas, Monilia and Haemophilus Vaginalis, the organism responsible for the so-called "non specific" infections.

Needs fewer applications and a shorter period of treatment.

Odourless.

Non-toxic.

No douching is necessary.

PRESENTATION

Sterisil is available in tubes sufficient for six applications and six disposable applicators are supplied in the same pack.

DOSAGE

Sterisil is effective for the treatment of all vaginal infections. It is recommended that a course of 12 applications be followed, even though a clinical cure may be achieved after six.

sterisil

VAGINAL GEL

WILLIAM R. WARNER & CO. LTD.

Intramuscular Iron

and the

Anaemias of Infancy

The value of Imferon in Nutritional Anaemia of Infancy and in the prophylaxis and treatment of Anaemia of Prematurity has recently been convincingly demonstrated.

- "There was obvious rapid clinical improvement in all cases as shown by the return of appetite, change of disposition, improvement in colour, and gain in weight."
- "The daily rise in haemoglobin during the first two weeks after treatment was almost 1.5%."—*Lancet*, 1955, 2 700.

Imferon is the most practical and effective means of administering iron to infants who do not make progress on oral preparations. The increase in haemoglobin concentration is about 20% in two weeks—more than can be achieved with any form of oral therapy.

THE INDICATIONS FOR IMFERON IN INFANCY ARE:

1 Nutritional anaemia in infants who do not make progress on oral iron.
2 Nutritional anaemia in infants whose home conditions are poor and who would otherwise have to be admitted to hospital.
3 The prophylaxis and treatment of anaemia of prematurity.
4 As an alternative in some cases to blood transfusion.

FURTHER INFORMATION IS AVAILABLE ON REQUEST

Imferon is issued in ampoules of 2ml. (100 mg. Fe) in boxes of 10 and 100.

Imferon REGD

IRON-DEXTRAN COMPLEX

A PRODUCT OF BENGER LABORATORIES

BENGER LABORATORIES LIMITED · HOLMES CHAPEL · CHESHIRE

INTRODUCING

sterisil

TRADE MARK

Active against all the common pathogenic organisms of the vagina including Trichomonas, Monilia and Haemophilus Vaginalis, the organism responsible for the so-called "non specific" infections.

Needs fewer applications and a shorter period of treatment.

Odourless.

Non-toxic.

No douching is necessary.

PRESENTATION

Sterisil is available in tubes sufficient for six applications and six disposable applicators are supplied in the same pack.

DOSAGE

Sterisil is effective for the treatment of all vaginal infections. It is recommended that a course of 12 applications be followed, even though a clinical cure may be achieved after six.

sterisil

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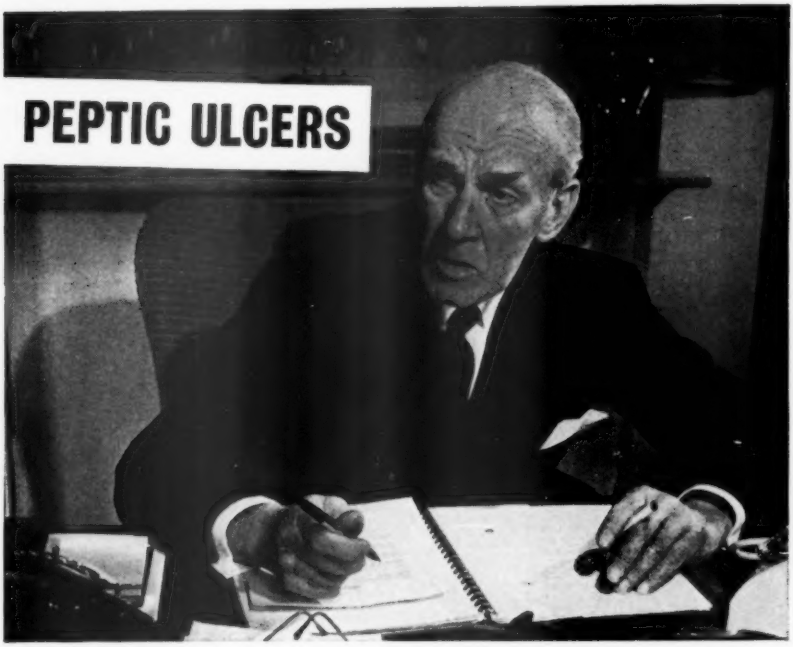

Pursuing his normal (pH) business

Benjamin McDougall, Esq., is a typical hard-pressed businessman. Year after year he carries a heavy burden of worrying responsibility. Peptic ulcers trouble him at intervals and the threat of them is always present.

A clear case for ALUPHOS TABLETS. Aluphos Tablets, alone of common antacids, buffer the gastric secretion to pH 2.0—2.5—a normal value at which peptic digestion is not inhibited. As a buffer, Aluphos Tablets act quickly, one or two tablets will remain effective for several hours.

Aluphos Tablets cannot cause 'acid rebound' and there is no risk of alkalosis. They are non-constipating.

Mr. McDougall will appreciate Aluphos Tablets because they are palatable, portable and efficient.

Aluphos Tablets are economical—the basic N.H.S. price is 2/7d. per box of 50 tablets.

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LOCAL ANAESTHESIA

INFILTRATION ANAESTHESIA demands a satisfactory spread of anaesthetic solution. It is especially valuable in the outpatient department in cases where general anaesthesia is contra-indicated.

A CLEAR CASE FOR HYALASE, the enzyme hyaluronidase.

HYALASE greatly enhances the spread and absorption of the anaesthetic. It can be easily combined with the local anaesthetic with or without adrenaline, producing a greater area of anaesthesia of satisfactory duration.

HYALASE can be successfully applied whenever infiltration anaesthesia is the method of choice.

FULLY-DESCRIPTIVE LITERATURE is available and a Technical Information Service is always at your disposal.

A clear case for HYALASE

TRADE MARK

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H.9

THIS CHILD is suffering from acute otitis media. The parents are anxious. Inflammation and pain must be relieved and infection controlled.

A CLEAR CASE FOR AURALGICIN. Auralgicin—widely known, trusted and prescribed — alleviates pain, reduces the incidence of complications, promotes drainage and encourages resolution. It is quickly and easily administered. Instruction leaflets for the guidance of patients can be supplied to prescribers.

FULLY DESCRIPTIVE literature is available and a Technical Information Service is always at your disposal.

A clear case for **AURALGICIN**
TRADE MARK

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A.3.

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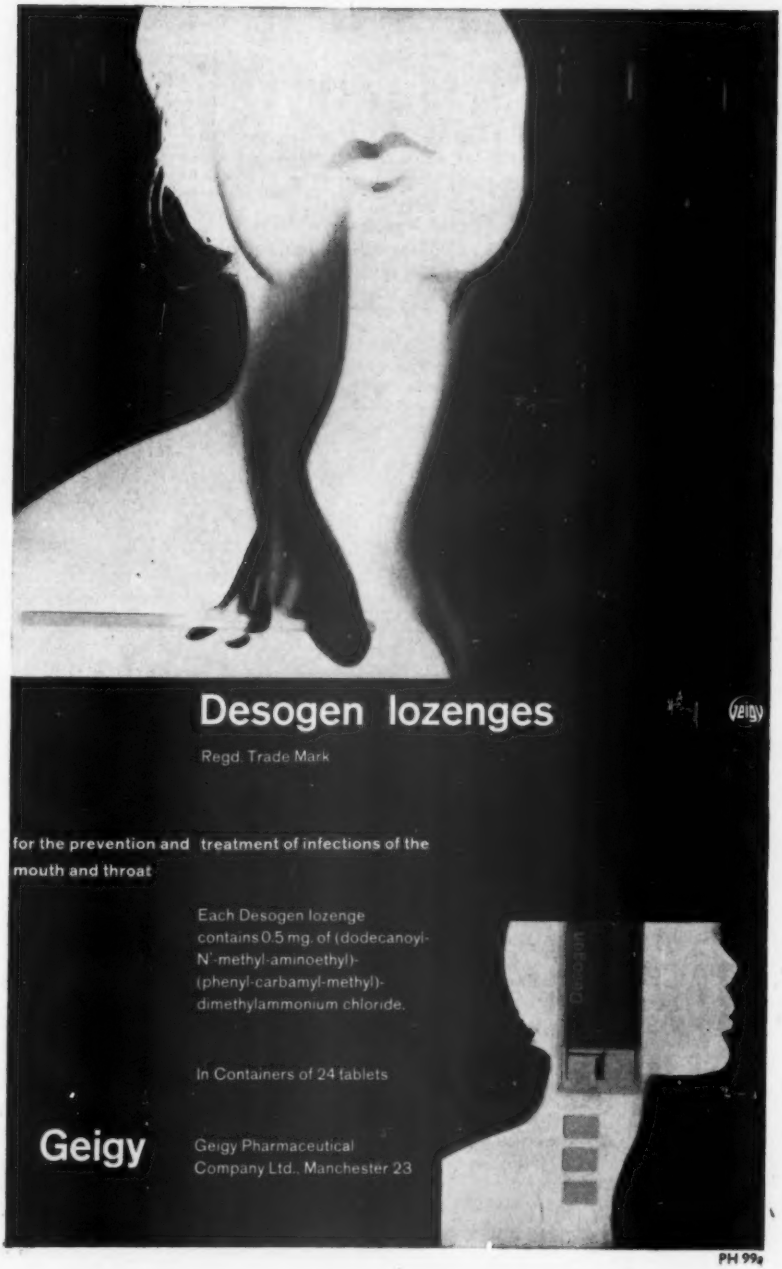
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Regd. Trade Mark
Geigy
for the prevention and treatment of infections of the mouth and throat
Each Desogen lozenge contains 0.5 mg. of (dodecanoyl-N'-methyl-aminoethyl)-(phenyl-carbamyl-methyl)-dimethylammonium chloride.
In Containers of 24 tablets
Geigy
Geigy Pharmaceutical Company Ltd., Manchester 23
Desogen
PH 99a

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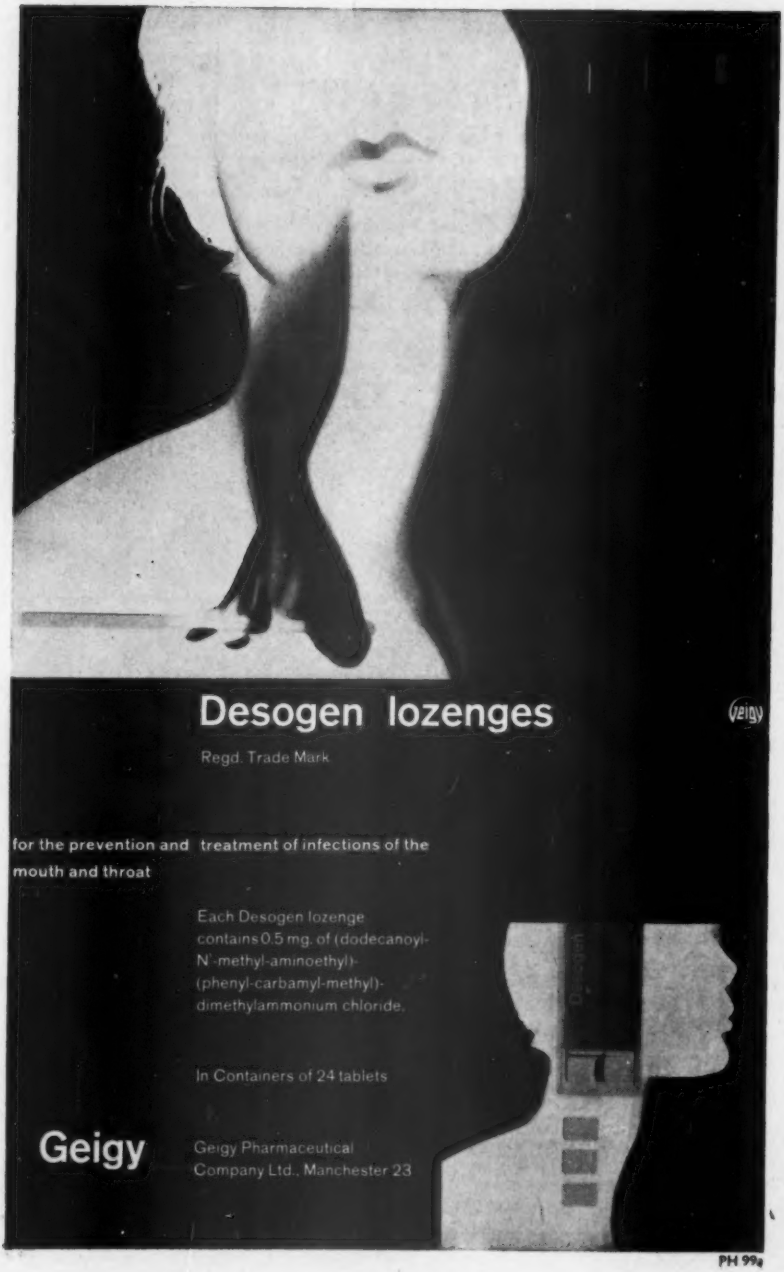
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ADVERTISED AND INTRODUCED *ONLY* TO THE MEDICAL PROFESSION

PULMO BAILLY

Constituents	*Properties*
GUAIACOL . .	Antiseptic, Leucocytogenetic and Expectorant
CODEINE	Cough Sedative
PHOSPHORIC ACID	Tonic and Restorative

PULMO-BAILLY restrains Broncho-pulmonary infection, facilitates elimination of bronchial secretions, soothes irritating and fatiguing cough, restores appetite, nervous and physical tone.

IMPORTANT IN
BRONCHITIS AND BRONCHO-PULMONARY AFFECTIONS, INFLUENZA, BRONCHIECTASIS, TRACHEITIS, CHEST CONGESTION OF THE AGED

BASIC N.H.S. PRICES—90 c.c. bottle **2/10** plus **10d.** P. Tax.
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ASTHMA

Instant relief!

Ever increasing numbers of medical men are relying on Rybarvin Inhalant to combat bronchospasm. The Ministry of Health having agreed to the prices of Rybar asthma inhalants, Rybarvin can be freely prescribed.

RYBARVIN brings relief. Consistently, often spectacularly, attacks are cut short and their frequency lesssened. Free from excess acid, non-irritant and non-habit-forming it is an ideal inhalant for all asthmatics young and old.

RYBAR INHALER has been specially designed for aerosol therapy.

Other RYBAR Products for asthma include **RYBAREX** Inhalant for cases complicated by Bronchitis and **RYBRONSOL** Powder, an ideal sedative. All, including the Inhaler, may be prescribed on N.H.S. Form E.C.10.

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Rybarvin Formula

Pituitary Extract. Posterior and Anterior Lobe	0·40% w/v
Methylatropine Nitrate	0·14% w/v
Papaverine	0·08% w/v
Adrenaline	0·40% w/v
Ethyl Para-aminobenzoate . .	0·20% w/v
Iso-butyl Para-aminobenzoate	0·01% w/v

RYBAR
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TANKERTON · KENT
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Aspirin *and* Ulcer

"ASPIRIN is a serious gastric irritant, particularly in peptic ulcer patients."

"Calcium aspirin does not have this irritant action unless it has deteriorated through standing, and it can be used with impunity, especially if prescribed in soluble form. This simple measure would, in our opinion, cut down significantly the incidence of hæmatemesis and exacerbations of ulcer symptoms."

British Medical Journal, July 2nd 1955

SOLPRIN provides calcium aspirin in pure and stable form

CODIS is a compound tablet that provides codeine and phenacetin and calcium aspirin, in place of the ordinary aspirin in Tab. Codein. Co. B.P.

Neither SOLPRIN nor CODIS is advertised to the public

RECKITT & COLMAN LTD., HULL & LONDON (PHARMACEUTICAL DEPT., HULL)

Between the 'up' and the 'about'

Serious illness is inevitably followed by a frustrating period of convalescence. Metatone,* with its stimulating, appetite-promoting combination of vitamin B_1 with strychnine and mineral glycerophosphates is ideally suited for the rapid restoration of normal metabolic function. It is specially valuable after 'flu and similar debilitating illnesses, after surgical operations, in neurasthenia and during pregnancy and lactation.

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Each fluid ounce of Metatone contains:

Vitamin B_1	3 mg.
Calcium Glycerophosphate	4 gr.
Potassium Glycerophosphate	4 gr.
Sodium Glycerophosphate	2 gr.
Manganese Glycerophosphate	½ gr.
Strychnine Glycerophosphate	8/200 gr.

METATONE

*Trade Mark

Parke, Davis & Co. Ltd., (*Inc. U.S.A.*) HOUNSLOW, MIDDLESEX
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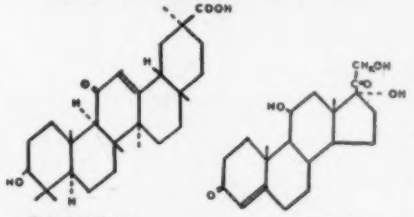
A new anti-inflammatory and anti-pruritic agent

BIOSONE G.A.

BIOSONE G.A. PREPARATIONS contain the active isomers of Glycyrrhetinic Acid which, when applied to the skin, has an action resembling that of HYDROCORTISONE (B.M.J., Dec. 1955, p. 1501, LANCET, July 1956, p. 145).



Glycyrrhetic Acid
Glycyrrhetinic Acid

Hydrocortisone

Available as :—

BIOSONE G.A. Ointment "GREASY"

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BIOSONE G.A. SNUFF

BIOSONE G.A. is INEXPENSIVE by comparison with Hydrocortisone and no systemic or local reactions have been reported.

BIOSONE G.A.

The FIRST CHOICE in the treatment of inflammatory conditions

FREELY PRESCRIBABLE ON E.C.10

Samples and literature available on request.

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BIOREX (MARKETING) LTD.

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VALOXYLIN

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Whole liver extract reinforced with vitamin B12

For the treatment of pernicious anaemia with or without neurological manifestations and for those other types of macrocytic anaemia which also respond to liver therapy. For sprue and as a general tonic.

Literature and prices on request.

AN OXOID PRODUCT

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DIGITALINE NATIVELLE

The digitoxin of choice, appreciated for its trustworthiness, its high and constant activity, as shown by standard works on cardiology and extensive clinical practice.

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TABLETS (pink) 0.1 mg (1/600 gr.)
TABLETS (white) 0.25 mg (1/240 gr.) } (Bottles of 40 and dispensing packs of 200)
AMPOULES 0.2 mg (1/300 gr.) for i.v. or i.m. injection. (Boxes of 6)

Samples and literature on request. *Exempt from Purchase Tax.*

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74-77 White Lion St., LONDON, N.1 18-19 Temple Bar, DUBLIN

. . . IN DANDRUFF A SINGLE WEEKLY TREATMENT IS NORMALLY SUFFICIENT TO ENSURE COMPLETE CONTROL

SEBODERM

CETRIMIDE SHAMPOO

MASTERS DANDRUFF

SEBODERM contains 15.6% Cetrimide B.P., the quaternary ammonium proved by research and prescribed by the medical profession as most effective in the specific treatment of dandruff and the more serious seborrhoeic dermatitis.

" . . . perhaps the most valuable recent addition to therapy (of scurf or dandruff) has been the introduction of detergents such as cetrimide, which may be used alone or incorporated in shampoos, soaps or lotions."
(1956) *Brit. Med. J.*, ii, 92.

SEBODERM also contains 15.6% Cetyl Alcohol B.P. and 1% Lanolin, and as a creamy and pleasing shampoo leaves the hair soft, silky and clean.

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PRIORY LABORATORIES LTD. PYRAMID WORKS · WEST DRAYTON · MIDDX.

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INCREASED SAFETY

AND EFFICIENCY WITH

HYDROMYCIN

IN THE TREATMENT OF INFLAMMATORY SKIN CONDITIONS

HYDROMYCIN by combining the anti-inflammatory properties of Hydrocortisone with the anti-bacterial properties of Neomycin offers increased safety over the use of Hydrocortisone alone. HYDROMYCIN is ideal in the treatment of contact dermatitis, atopic dermatitis and non-specific pruritus.

SKIN OINTMENT *Tubes of 5 G and 15 G*

EAR/EYE OINTMENT *Tubes of 3 G*

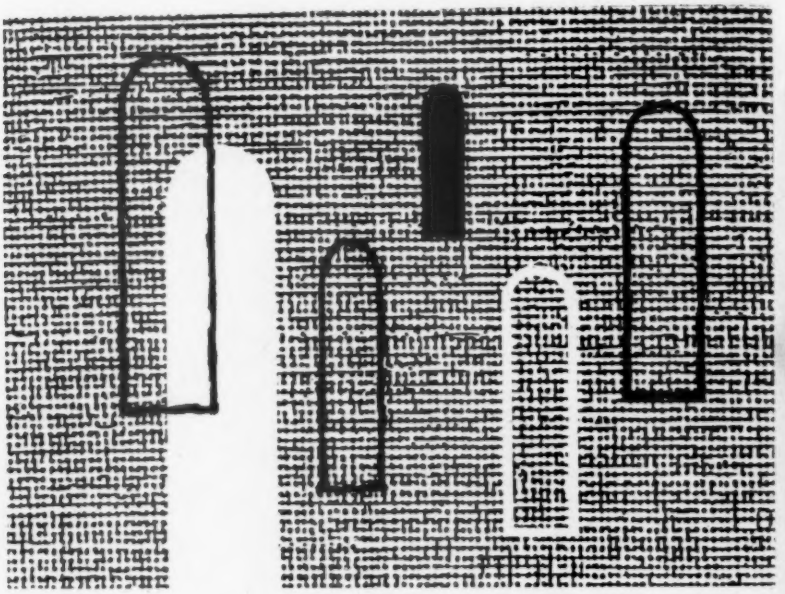
THE FULL RANGE OF BOOTS BRITISH-MADE CORTI-COSTEROIDS

CORTISTAB (Cortisone Acetate) Tablets, Injection, Eye Drops, Eye Ointment.
HYDROCORTISTAB (Hydrocortisone) Tablets, Local & Intravenous Injections, Skin Ointment, Eye Ointment, Eye Drops.
DELTA-STAB (Prednisolone) Tablets.
Delta-stab Tablets are at present available through N.H.S. hospitals only by arrangement with the Ministry of Health.

Literature and further information gladly sent on request:

BOOTS PURE DRUG COMPANY LIMITED, NOTTINGHAM

Boots



the shape of relief . . .

The shape of a haemorrhoidal suppository is almost as important as the nature of its active ingredients.

The cylindrical shape of ANUSOL suppositories facilitates pain-free insertion and easy retention.

An ANUSOL suppository melts rapidly, bringing soothing and healing medicaments to a wide area of inflamed rectal mucosa.

Active principles: Bismuth subgallate 2.12%, bismuth oxyiodogallate 0.03%, bismuth oxide 0.87%, resorcin 0.87%, balsam of Peru 1.77%, zinc oxide 10.60%, boric acid 17.85%, base of cacao butter and beeswax q.s. ad. 100.00%.

Packing: Ointment: 1 oz. tubes. Suppositories in boxes of 12; also boxes of 100 for dispensing purposes.

ANUSOL
TRADE MARK

WILLIAM R. WARNER & CO. LTD. · POWER ROAD · LONDON, W.4

Ortho

new

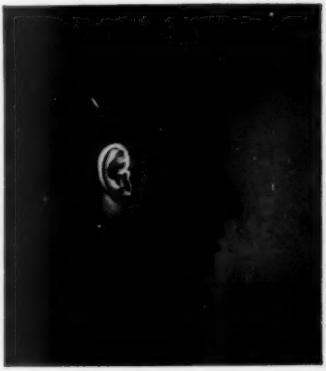
The unmatched potency of **Delfen** vaginal cream is due to its new chemical spermicidal agent which invades every vaginal crevice by the rapid release action of a new emulsified oil-in-water base

Delfen vaginal cream:
nonylphenoxypolyethoxyethanol 5.00%
in an oil-in-water emulsion at pH 4.5
LITERATURE ON REQUEST

Ortho Pharmaceutical Limited · High Wycombe · England

EAR WAX

Removed this easy way



The removal of wax from the external auditory meatus has, in the past, normally entailed attendance by the patient for diagnosis and for the prescription of a suitable loosening agent, and a second attendance a few days later for syringing.

Now, by the use of Cerumol Ear Drops, wax can be removed in most cases at one visit. A few drops of Cerumol can be instilled into the ear and, while another patient is being attended to, the soft cerumen dissolves and the harder wax disimpacts. The wax can then be removed by gentle syringing or with cotton wool. The wax may even be found to run out of the ear on its own accord, in which case patients themselves may instil Cerumol at home, obviating further attendances.

Cerumol is anti-bacterial, non-irritating and harmless to the lining of the external auditory meatus or the tympanic membrane.

Cerumol is included in Category No. 4 of the M.O.H. classified list and may be prescribed on N.H.S. Form E.C.10.

CERUMOL
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EAR DROPS

for the easier removal of wax

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If you wish to test for yourself and have not received recently a 10. c.c. vial please write or telephone direct to :

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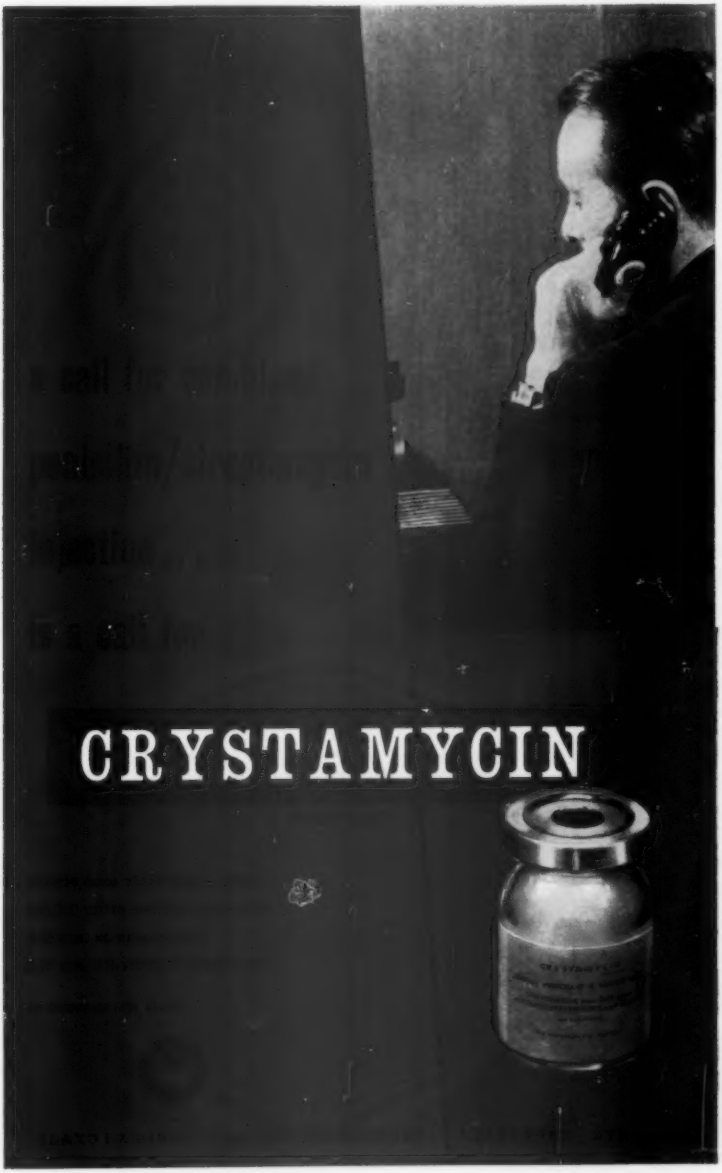
PACKS For Surgery Use : 10 c.c. vial — separate dropper included (Basic N.H.S. price 2/8) for Hospital Use : 2 oz. and 10 oz. bottles.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Pixcyl and Psorox

Coal Tar has long been accepted as one of the most effective medicaments for use as a topical application in the treatment of Psoriasis.

The Genatosan tar fractions incorporated in Pixcyl, Psorox, Genisol and Sebigen, offer tar therapy without many of the disadvantages associated with crude coal tar. Extensively screened against sensitization and in bases to suit each phase of the disorder, they offer the physician the three essential factors in his choice of an effective topical application that combine to give a suitable approach to Psoriasis.

Pixcyl, Psorox, Genisol and Sebigen
are all available on E.C.10.

Further information available from:
Genatosan Ltd., Loughborough, Leicestershire

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BENZEDREX INHALER

replaces
Benzedrine
Inhaler

Benzedrex Inhaler is effective 'Benzedrex' Inhaler provides initial relief from nasal congestion within seconds. Five minutes after inhalation shrinkage of the nasal mucosa is complete. Even with gross engorgement shrinkage remains adequate for over 1½ hours.

Benzedrex Inhaler is specific The active ingredient in 'Benzedrex' Inhaler is a new compound—propylhexedrine—that is remarkable for its highly specific vasoconstrictive action. Unlike amphetamine, propylhexedrine produces virtually no central nervous stimulation.

Benzedrex Inhaler is safe Because its vasoconstrictive action is uncomplicated by central nervous stimulation, 'Benzedrex' Inhaler may be freely used even by those patients in whom sympathomimetic drugs often cause insomnia, restlessness or nervousness. Even massive overdosage does not result in central nervous stimulation.

NEW AND BETTER... BENZEDREX INHALER

SKF's new and better volatile vasoconstrictor

Smith Kline & French represented by Menley & James, Ltd., London S.E.5 Tel: BRIxton 7722

'Benzedrex' and 'Benzedrine' are registered trade marks

BXP106 (col)

In two years Becantyl has become an established treatment for useless cough–

Especially with children and old people. No side-effects

Unrelated to morphine derivatives or guaiacol and with none of their disadvantages, Becantyl suppresses useless cough. The active ingredient in Becantyl is Sodium-2: 6-ditertiarybutylnaphthalene monosulphonate. This chemical, which does not cause constipation, anorexia, drowsiness or other side-effects, is the result of original research.

These characteristics make Becantyl especially valuable for the treatment of useless cough in children and old people.

Becantyl is available in 4 fluid-ounce bottles, and also in 40 fluid-ounce and 80 fluid-ounce dispensing bottles.

The suggested doses are:—

Adults: 2 teaspoonfuls

Children: 3—6 years: ½ teaspoonful
7—15 years; ½—1 teaspoonful
three times a day or as prescribed.

Becantyl has no B.P. or N.F. equivalent, is not advertised to the public, and may be prescribed on form E.C.10.

BECANTYL

Literature and Samples available from the Medical Information Department
Horlicks Limited, Pharmaceutical Division, Slough, Bucks.

BIBLIOGRAPHY

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A propos des Sédatifs de la toux. *Revue du Praticien*, 1954, No. 7

An assessment of Roter therapy in

PEPTIC ULCER

"The treatment is ideal for general practice, where its simplicity appeals to both patient and doctor . . ."

Results

"The immediate clinical results were assessed after the first month's treatment in four main groups: (A) pronounced relief (symptom free); (B) definite relief (minor symptoms with no pain); (C) doubtful relief (symptoms persisting but improved); (D no relief.

"Table II shows that 81% of cases became symptom-free—70% of them during the first week and 30% during the second week; a further 9% were relieved of the majority of their symptoms. Thus there was a satisfactory response in 90% of cases

TABLE II

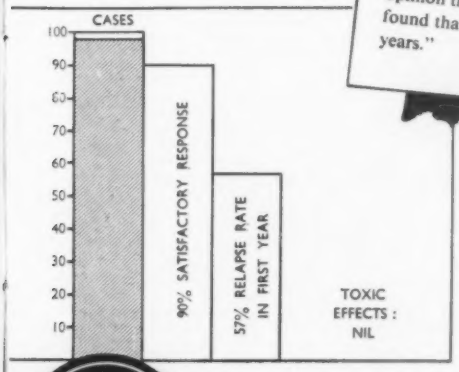
Group	Active Ulcers	Presumptive Ulcers	Totals
A	63 (79.6%)	17 (89.0%)	80 (81.7%)
B	8 (10.2%)	1 (5.5%)	9 (9.2%)
C	6 (7.6%)	1 (5.5%)	7 (7.1%)
D	2 (2.5%)	0 (—)	2 (2.0%)
TOTALS	79 (100%)	19 (100%)	98 (100%)

"Four of the nine cases in groups C and D have elected to go to surgery, and one of the remaining cases has a hiatus hernia as well as a duodenal ulcer. Experience of treating these "Failures" over the past six years leads one to believe that no form of medical treatment will be effective and that surgery is the only hope of relieving their symptoms. In 75% of cases the patients were of the opinion that the tablets were superior to alkaline powders, and they found that they were able to take foods which they had avoided for years."

Roter Tablets contain a balanced content of recognised buffers with supportive carminative and mildly laxative agents.

FORMULA PER TABLET

Magnesium Carbonate (400 mg.), Bismuth Subnitrate (350 mg.), Sodium Bicarbonate (200 mg.) Rhizoma Calami (25 mg.), and Cortex Rhamni Frangulae (25 mg.).



Extracts from the
BRITISH MEDICAL JOURNAL
1955, 2, 827

Summary

"Seventy-nine cases of peptic ulcer and 19 of presumptive peptic ulcer have been treated with Roter tablets. Immediate clinical response was satisfactory in 90% of patients, with a relapse rate of 57% in the first year: a reduction in the average number of relapses was recorded in 15 cases kept on a maintenance dose for one year."

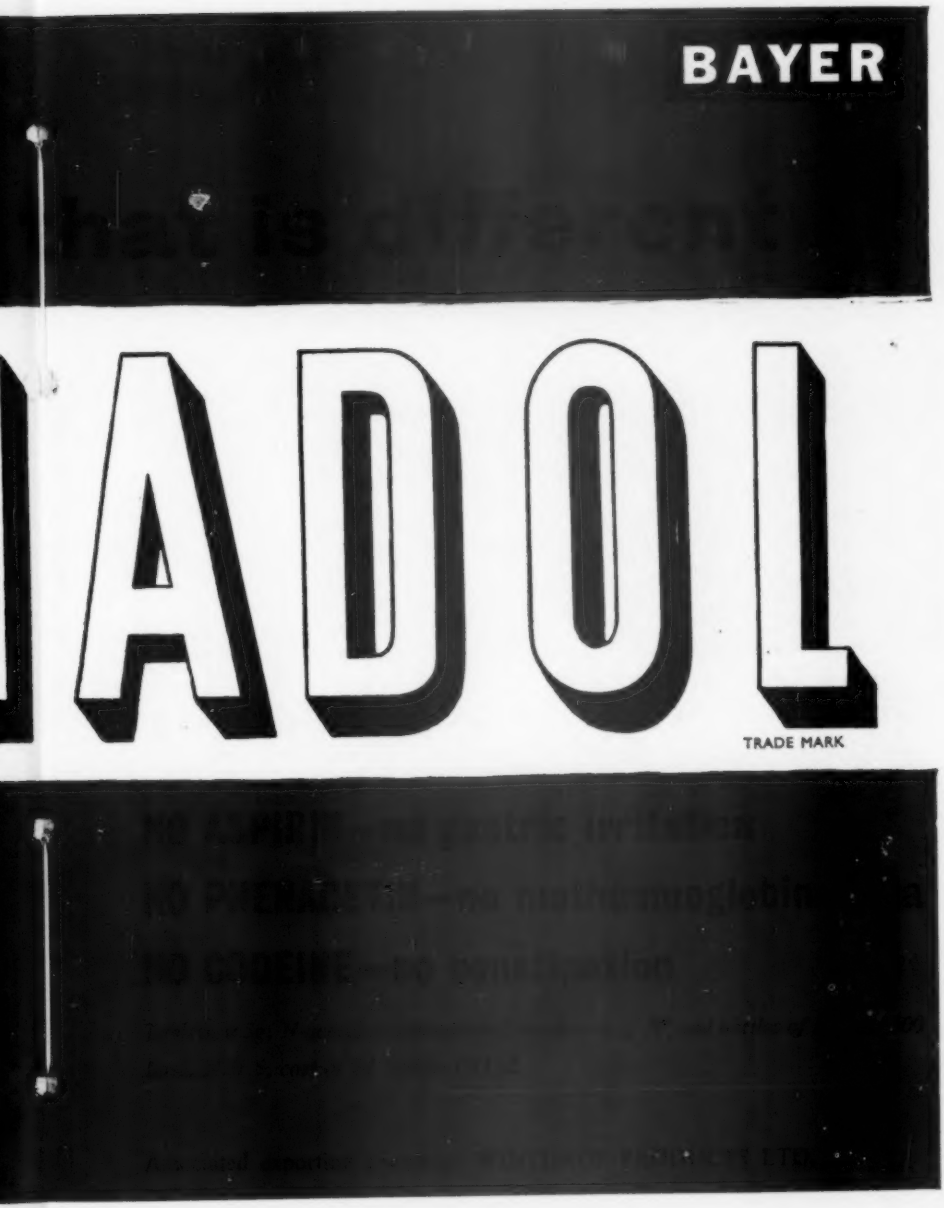
Packings: Tins of 40, 120, 640, and dispensing size 720 (P.T. exempt).

Roter Tablets are not advertised to the public and may be prescribed on E.C.10 forms. Literature and samples on request.

ROTER **TABLETS**

F.A.I.R. LABORATORIES LTD., TWICKENHAM, MIDDLESEX.

PANA
BAYER


BAYER
ADOL
TRADE MARK

You can use

Elastoplast Plaster...

...On its own

* to strap a dislocated thumb. One-inch Elastoplast Plaster is used, applied spica-fashion.

* to cover impetigo lesions, allowing undisturbed self-healing.

...Or to keep a dressing in place

* in cases where it is preferable to cut an individual strip rather than to use a ready-made first-aid dressing.

ELASTOPLAST PLASTER is flesh-coloured, made from light-weight cloth, and ideal for on-the-spot strapping and retention of dressings. It is far more comfortable and more efficient than a rigid plaster.

ELASTOPLAST: *elastic adhesive plaster B.P.C.*
1″ or 2″ x 1¾/2 yds stretched and 1″ x 5/6 yds stretched

WATERPROOF ELASTOPLAST *Plaster*
plastic strapping 1″ x 1 yd and 1″ or 2″ x 3 yd

SMITH & NEPHEW LTD · WELWYN GARDEN CITY · HERTS

Outside the British Commonwealth Elastoplast is known as ***Tensoplast***

S&N

1

Ventilate

Orthoxine possesses twice the bronchodilating and ventilating power of ephedrine—but only a fraction of ephedrine's cardiac, vasopressor ($\frac{1}{8}$) and CNS stimulating effect. This well-tolerated agent efficiently relaxes the spasm that *is* cough and assures optimal ventilation to help sweep mucus out of the bronchial tree. Equally important, Orthoxine does not make the patient restless or rob him of sleep

2

Sedate

Reducing sensitivity of the cough reflex, codeine phosphate breaks the vicious cycle of cough—irritation—cough. Tenacious bronchial secretions are liquified by sodium citrate without producing nausea

For physiological cough-control:

ORTHOXICOL*

Orthoxicol combines the exclusive Upjohn—amine Orthoxine* with codeine phosphate and sodium citrate for "two-way" physiological cough control

**Dosage:*

Infants: (2 to 6 months) 3 to 6 drops every four to six hours
(6 to 12 months) 6 to 10 drops every four to six hours
(1 to 2 years) 10 to 20 drops every four to six hours

Children: (2 to 12 years) ½ to 1 teaspoonful every four hours

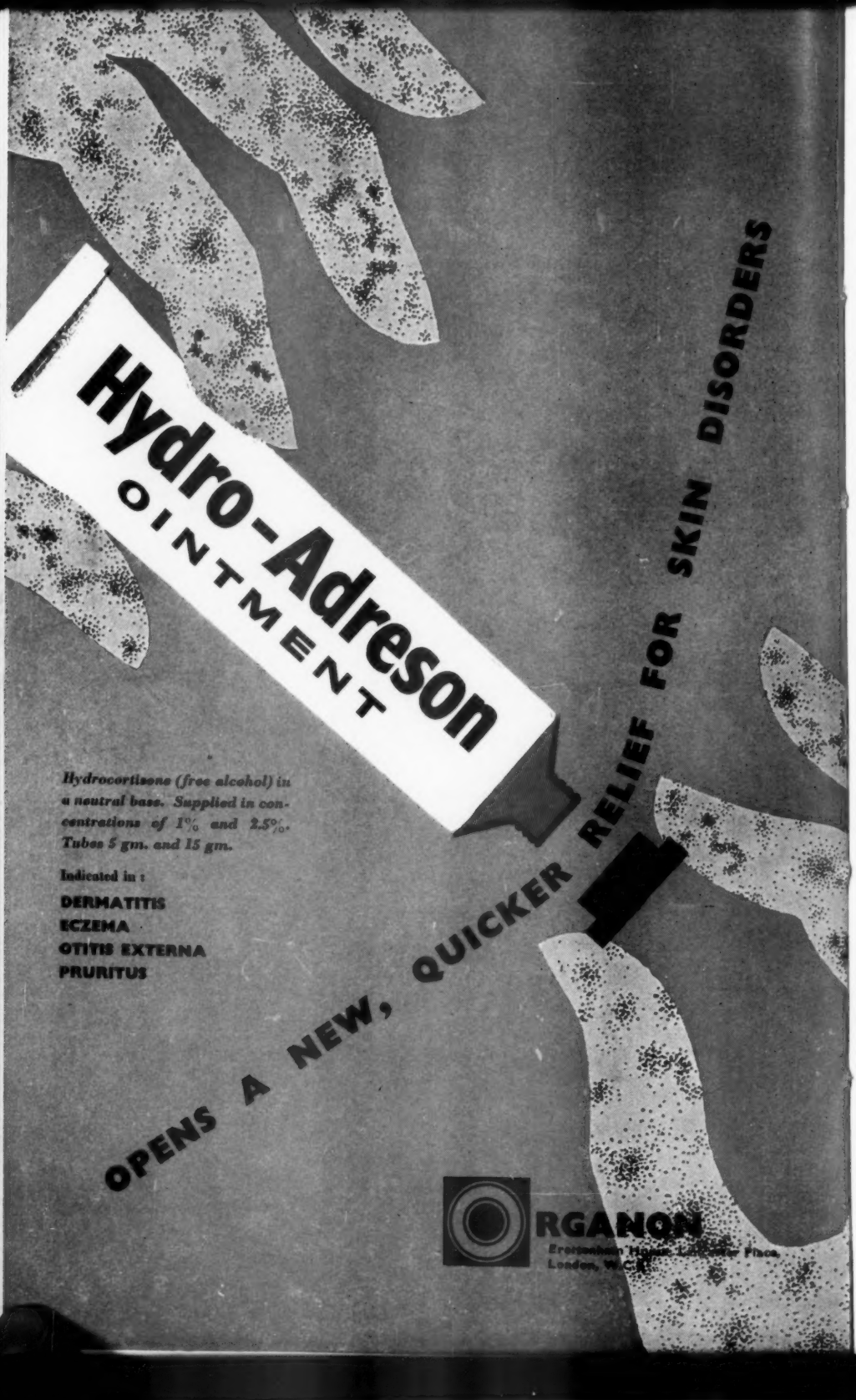
Adults: 1 to 2 teaspoonfuls every three or four hours

Supplied:
in bottles of 2 and 16 ounces

*Registered Trade Mark

Upjohn

UPJOHN OF ENGLAND LTD
4 ALDFORD STREET · LONDON W1


Hydro-Adreson
OINTMENT
OPENS A NEW, QUICKER RELIEF FOR SKIN DISORDERS
Hydrocortisone (free alcohol) in a neutral base. Supplied in concentrations of 1% and 2.5%. Tubes 5 gm. and 15 gm.
Indicated in :
DERMATITIS
ECZEMA
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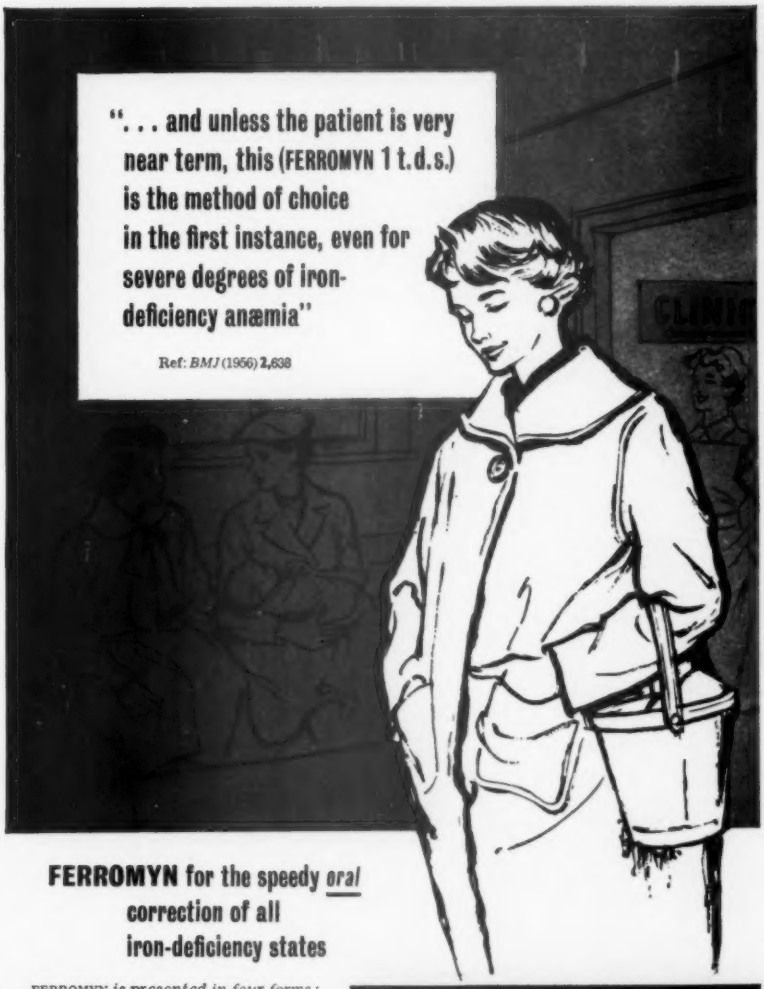
Bretonham House, Lancaster Place
London, W.C.2


". . . and unless the patient is very near term, this (FERROMYN 1 t.d.s.) is the method of choice in the first instance, even for severe degrees of iron-deficiency anæmia"
Ref: BMJ (1956) 2,638
CLINIC

FERROMYN for the speedy *oral* correction of all iron-deficiency states

FERROMYN is *presented in four forms:*
FERROMYN TABLETS AND FERROMYN ELIXIR.
Each tablet/teaspoonful contains:
Ferrous Succinate 150 mg.
FERROMYN 'B' TABLETS AND ELIXIR FERROMYN 'B'.
Each tablet/teaspoonful contains:
Ferrous Succinate 150 mg. Aneurine Hydrochloride 1 mg. Riboflavin 1 mg. Nicotinamide 10 mg.

FERROMYN

CALMIC LIMITED, CREWE
Phone CREWE 3251-5

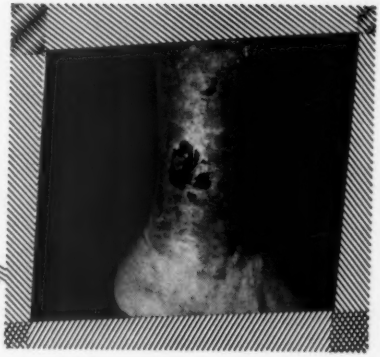
LONDON:
2 Mansfield St., W.1. Phone LANgham 8038-9

AUSTRALIA: 458-468 Wattle St., Ultimo, Sydney. N.S.W. **CANADA:** Terminal Building, York St., Toronto.

T5

The use of stabilized Trypsin

A NEW TREATMENT FOR **ULCERS** **ABRASIONS** **BURNS** **PYODERMIAS**



ANY MEDICAL PRACTITIONER knows how stubbornly resistant to any therapy a long-standing varicose ulcer can be. The reason is partly the diminished blood supply, but more perhaps the formation of a pus-containing layer and of crusts which cover the ulcer and impede the healing process. Similar difficulties are often encountered in the treatment of wounds and abrasions.

PROTEOLYTIC ACTION

It has long been known that the proteolytic enzyme Trypsin could digest crusts by the process of physiological currettage. The difficulty has been to incorporate the trypsin in a stable preparation. In Biotrase trypsin remains active physiologically for over one year. A certificate of stability has been issued by a leading Institute of Bio-chemistry. It rapidly dissolves crusts and scabs and leaves a clean. granulating surface.

Biotrase has been designed by Lloyd-Hamol of London and Zurich for the treatment of infected skin lesions. Apart from trypsin, it contains two new antiseptic agents of proved bacteriolytic properties, Ca-N-Hydroxymethylglutaminate and 2,2¹ thiobis-(4,6-dichlorophenol) designated bithionol, both of which are effective against a wide range of gram-positive and gram-negative pathogenic organisms and do not cause skin sensitivity. Biotrase also contains Carbamide, included for its buffering properties.

INDICATIONS FOR USE

Biotrase may be used wherever there is an infected—or potentially infected—breach of surface of the skin. Common conditions for its use include the following: Varicose, diabetic and post-thrombotic ulcers; wounds, and second and third degree burns; infected and necrotic skin conditions, including pyodermias; boils and carbuncles (following incision).

COMPOSITION OF BIOTRASE

Trypsin pur.	0.16%
Ca-N-Hydroxymethylglutaminate	5.00%
2,2¹ *thiobis-(4,6-dichlorophenol)*	0.50%
Carbamide B.P.	5.00%
In polyethylene glycol	

Biotrase

Biotrase is available in 35g. tubes at a basic N.H.S. price of 3/9d. plus Purchase Tax. Samples and literature are available to medical practitioners on request.

'Biotrase' is a registered trade mark of
LLOYD-HAMOL LIMITED
11 Waterloo Place, London, S.W.1.

Ortho DE-LUXE Kit

discreet, practical

complete prescription for conception control

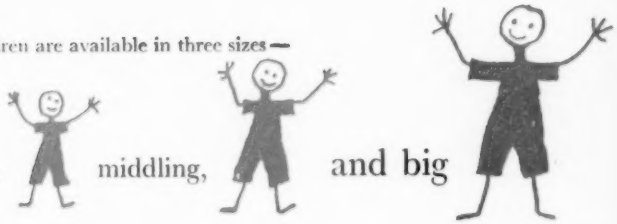
in washable, elegant and durable zipper bag of plastic yarn

Ortho

Ortho Pharmaceutical Limited · High Wycombe · England

Eskacillin

Children are available in three sizes—



little, middling, and big

'Eskacillin' is available in three strengths—100, 200, and 300.

If you match the strength of 'Eskacillin' to the size of the child you can prescribe simply 2 standard medical teaspoonfuls t.i.d.

Very simple. Kid's stuff, really.

under 8 Eskacillin 100
8–14 Eskacillin 200
over 14 Eskacillin 300
} 2 tsp. t.i.d.

the children's penicillin

Smith Kline & French *represented by* Menley & James, **Limited, London S.E.5**

EC:PA157 (Col)

POLYBACTRIN

antibiotic powder spray

INVALUABLE IN ALL BRANCHES OF SURGERY

Polybactrin provides a unique and economical means of applying a combination of Zinc Bacitracin, Neomycin Sulphate and Polymixin 'B' Sulphate—the three antibiotics of choice for topical use. The antibiotics are presented in an ultra-fine powder form dispersed under pressure with a propellant, and unlike other means of powder insufflation in common use, there is no risk of contamination of the antibiotics by airborne pathogens obtaining entry into the unit by suction.

A FRACTIONAL RELEASE GIVES COMPLETE DISPERSAL OF POWDER OVER THE WOUND

1. The *Polybactrin* unit offers a new technique for topical application of antibiotic therapy, enabling an efficient, economical and dry coverage of the wound area to be made.
2. The extensive range of bactericidal activity afforded by the triad of bacitracin, neomycin and polymixin gives an extremely wide coverage of wound pathogens without the risk of inducing resistant strains of organisms.
3. Ps. pyocyaneus, particularly present in burns, is completely inhibited by polymixin, considerably reducing the healing time.
4. *Polybactrin* is not readily absorbed and there is no risk of systemic toxicity occurring.
5. The propellant gas is non-toxic and does not support combustion.
6. There are no contra-indications to the use of *Polybactrin*. Systemic therapy may be given concurrently if necessary.

FORMULA: Each pack contains: Neomycin Sulphate 750 mg. Polymixin 'B' Sulphate 150,000 units. Zinc Bacitracin 37,500 units. Propellent 83·5 g. Net contents 85 g.

POLYBACTRIN antibiotic powder spray

Supplies initially for Hospitals only—no samples available.

CREWE: *Telephone: Crewe 3251-3*

CALMIC LIMITED

LONDON: *3 Mansfield Street, W.1 Tel: LANgham 6030-9*

AUSTRALIA: 458-468 Wattle St., Ultimo, Sydney, N.S.W. **CANADA:** Terminal Building, York St., Toronto

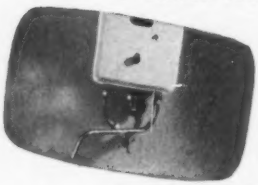
P.1

Clean hands

Adequate washroom facilities are essential to combat disease in the hospital, factory and office—and vital for clean food. Sometimes the demand is for large quantities of hot water continuously, day and night—or maybe it is needed instantaneously at irregular times. But whatever the hot water requirement, the Heating Engineers at your Area Gas Board have had considerable experience in fitting thousands of different hot water installations and will gladly advise you on your problem.

WHATEVER YOUR BUSINESS—**The Gas Industry appreciates the needs of individual consumers for prompt service and for advice which accords with the customer's special circumstances and requirements. Each Area Gas Board offers efficient service to users of gas-fired equipment and can give expert advice based upon the pooled knowledge of all the Boards and of gas users in other countries**

—CONSULT YOUR AREA GAS BOARD



ISSUED BY THE GAS COUNCIL

THE GAS INDUSTRY MAKES THE BEST USE OF THE NATION'S COAL

Milk-alkali drip therapy without a tube

NULACIN

The most effective control of gastric acidity is by milk-alkali drip therapy; the most convenient way of obtaining milk-alkali drip therapy is by sucking Nulacin tablets.

Thus, Nulacin is of great value in the treatment of peptic ulcer in the ambulatory patient, and in the prevention of ulcer relapse.

Nulacin tablets are prepared from whole milk combined with dextrins and maltose, and incorporate Magnesium trisilicate 3.5 grs; Magnesium oxide 2.0 grs; Calcium carbonate 2.0 grs; Magnesium carbonate 0.5 grs; Ol. menth. pip. q.s. Their shape, size and consistency are such that, when they are allowed to dissolve slowly in the mouth, control of gastric acidity can be achieved. Up to three tablets an hour may be required to give continuous neutralization of the gastric contents.

Nulacin tablets are not advertised to the public, have no B.P. equivalent, and may be prescribed on E.C.10. The dispensing pack of 25 tablets is free of Purchase Tax. (Price to Pharmacists is 2/-.) Also available in tubes of 12.

Nulacin is available throughout the British Commonwealth, in the U.S.A. and in many other countries. It is known as Nulactin in Canada and Sweden.

BIBLIOGRAPHY:

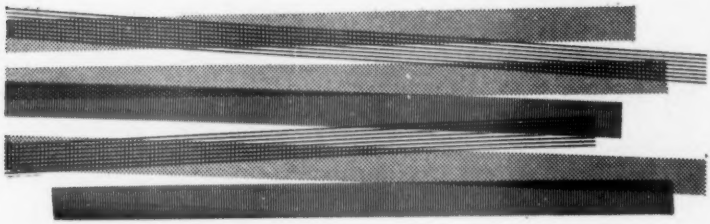
The Control of Gastric Acidity. *Brit. Med. J.* 26th July, 1952, **2**: 180-182. Medical Treatment of Peptic Ulcer. *Med. Press* 27th February, 1952, **227**: 195-199. Notes on Remedial Agents. *Med. Rev.* September, 1952, **46**: 162. Discussion on Peptic Ulceration. *Proc. Roy. Soc. Med.* May 1953, **46**: 354. The Effect on Gastric Acidity of "Nulacin" tablets. *Med. J. Aust.* 28th November, 1953, **2**: 823-824. Control of Gastric Acidity by a New Way of Antacid Administration. *J. Lab. Clin. Med.* 1953, **42**: 955. Further Studies on the Reduction of Gastric Acidity. *Brit. Med. J.* 23rd January, 1954, **1**: 183-184. Clinical Investigation into the Action of Antacids. *The Practitioner* July, 1954, **173**: 46. Management of Peptic Ulceration in General Practice. *Med. World* December, 1954, **81**: 591-601. Ambulatory continuous Drip Method in the Treatment of Peptic Ulcer. *Amer. J. Dig. Dis.* March, 1955, **22**: 67-71. Notes on Remedial Agents. *Med. Rev.* October, 1955, **49**: 142. Antacids in Peptic Ulcer. *The Practitioner*, January, 1956, **176**: 103.

Samples available on request

HORLICKS LIMITED

Pharmaceutical Division, Slough, Bucks

Stress



Peptic Ulcer personality?

Is there a "peptic ulcer personality"? Present opinions are conflicting, and its existence cannot therefore be accepted as fact. Nevertheless, the following are mentioned more frequently by various authorities* as being the most common traits of patients with peptic ulcer.

Anxiety Drive Conscientiousness Worry Hostility Ambition Persistence Meticulousness Tension Resentfulness Alertness Intelligence

THE BUSINESS EXECUTIVE

Although many of these character traits may naturally be discovered in the business executive, it does not necessarily follow that he will have peptic ulcer. But, because of the continual emotional strain attendant upon his position, the business executive would therefore seem more than usually prone to stress, and its various ensuing manifestations.

In the preventative treatment of these disorders, the fundamental importance of the simple psychotherapy which the General Practitioner is so well placed to dispense is beyond dispute. Yet he, himself, generally recognises the need for a more material adjunct; a tonic and restorative which will assist the nervous system as well as the organism as a whole.

Sanatogen is an active nutrient tonic, and the choice of many physicians in such circumstances. It contains 95% casein and 5% sodium glycerophosphate; because of its high nutrient and restorative effects on the nervous system, it can be recommended with assurance whenever a tonic is indicated, whether in general or mental asthenia, or in any condition of stress.

**A.M.A.Arch. Intern. Med.* (1955). *96*, 32.

Sanatogen

THE HIGH PROTEIN TONIC

The word 'Sanatogen' is a registered trade mark of Genatosan Limited, Loughborough, Leics.

IN THE MENOPAUSE

One bottle of 60 TACE capsules (2 capsules a day) can relieve many of your menopausal patients. Some may require a second course, but few will need a third.

Merrell

The introduction of TACE marks the beginning of a new era in the treatment of menopausal symptoms. TACE is stored in the body fat and subsequently released in a manner resembling normal hormone secretion. There is virtually no withdrawal bleeding (in four investigations [1, 2, 3, 4] there were only 7 cases of withdrawal bleeding in 257 patients) and TACE is also extremely well tolerated in other respects.

Because of fat storage the action of TACE is prolonged. In 13 out of 16 patients beneficial effects remained up to 4 months after therapy had been discontinued.

TACE is indicated in other cases which require œstrogen therapy—for example in the inhibition of lactation and the treatment of prostatic carcinoma.

TACE

is available in green capsules (each containing 12 mg. chlorotrianisene dissolved in oil) in bottles of 60 and 300.

1. *Wis. med. J.* (1954) 53:322.
2. *Amer. J. Obstet. Gynec.* (1954) 3:201.
3. *J. Indiana med. Ass.* (1954) 47:989
4. *J. Clin. Endocr.* (1954) 14:272.

Distributed in the United Kingdom and the Republic of Ireland by

RIKER LABORATORIES LIMITED, LOUGHBOROUGH, LEICS.

for the Wm. S. Merrell Company, London.

They like Lucozade..

and they can keep it down—

Lucozade has won its place in the sickroom because it is so very palatable. Patients enjoy it and, what is more, they can keep it down even when other food is refused, or vomited. It is difficult to assess the value of Lucozade simply in terms of the glucose it contains. It is the patient's response which is so interesting. Its acceptance so often coincides with a distinct and happy turn for the better, well illustrated in the following brief report:

"My little boy was ill . . . and was completely off his food. I must admit that I only thought of Lucozade at the last moment, after two days of worry, but he improved from the time of taking it."

LUCOZADE

the sparkling glucose drink

REPLACES LOST ENERGY

royds M 67/6

In Barbiturate Anaesthesia

SOME MEDICAL OPINIONS

'Megimide' rapidly terminates barbiturate anaesthesia without fasciculations or convulsions. 'Megimide' is a barbiturate antagonist of real clinical worth.

(1955) *Lancet*, i, 181

'Megimide' brings about a rapid recovery of consciousness in all cases of patients under light or deep barbiturate anaesthesia. Its greatest value is to reverse the depressant action on the respiratory centre. The use of 'Megimide' has simplified post-operative nursing of anaesthetised cases and is of particular value in a busy surgical ward, especially at night. We recommend its use in casualty, out-patient and dental surgery.

(1956) *Med. Proc.*, Vol. 2, No. 4 198

Megimide is of value to lighten or terminate the anaesthesia of patients under the influence of barbiturate anaesthetics. With its use, broncho-pneumonia, hitherto the commonest cause of death, is no longer a danger.

MEGIMIDE
Brand of Bemegride Registered Trade Mark

A. & G. NICHOLAS LTD.
Ethical Pharmaceuticals,
Buckingham Avenue, Slough, Bucks.
Telephone: Slough 22381/5.

for quick relief of abdominal SPASM†

BUSCOPAN is a safe and effective spasmolytic with a specific point of attack, relieving spasm smoothly without disturbing the patient's comfort. In all its uses, BUSCOPAN is rapid in action and free from atropine-like side effects.

MINIMUM SIDE REACTIONS

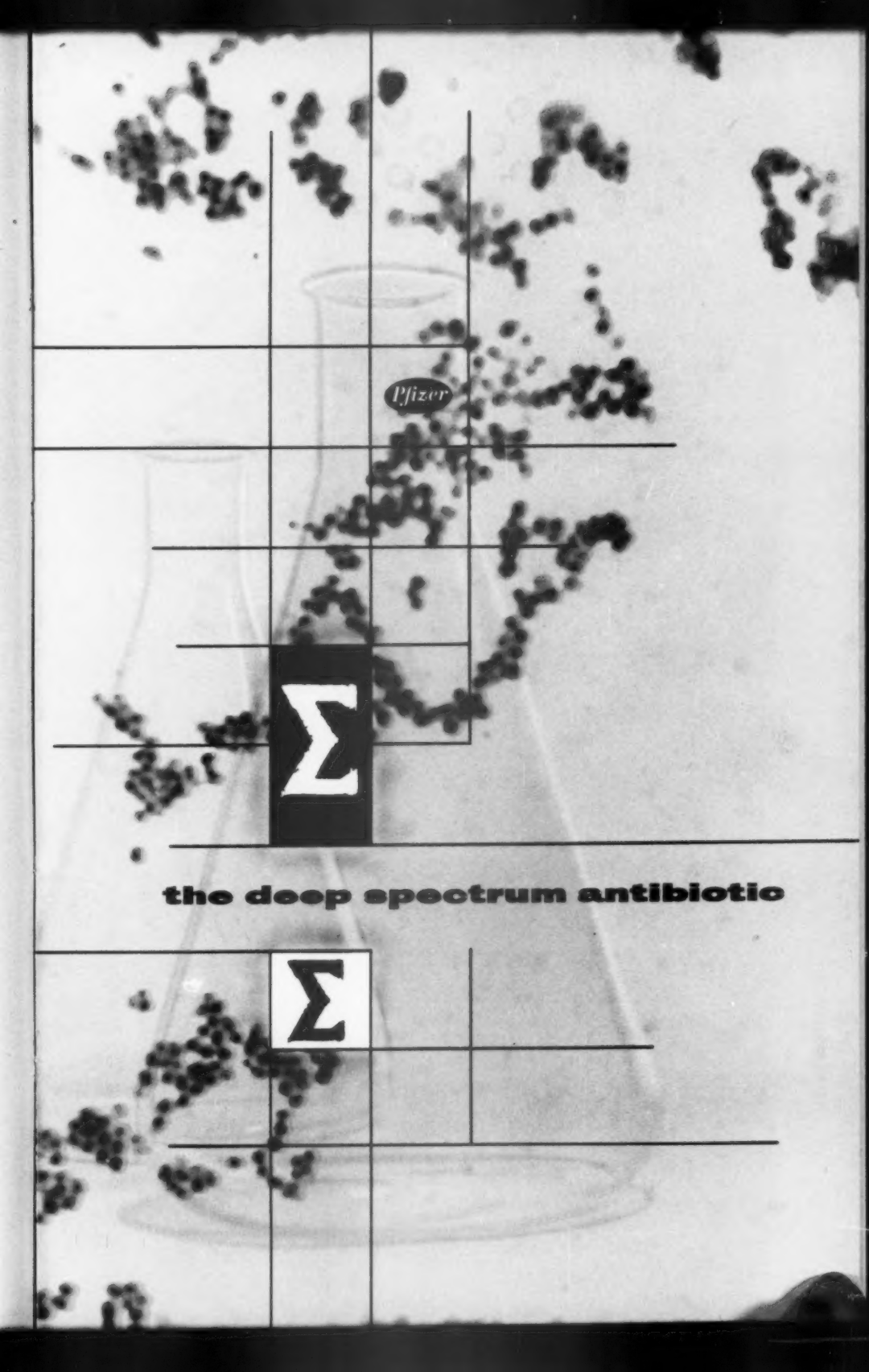
Acts safely and quickly without affecting blood pressure or heart.

†**relief from spasm can mean complete CURE**

BUSCOPAN* HYOSCINE-N-BUTYLBROMIDE

Registered Trade Mark

Manufactured and distributed in England by Pfizer Ltd., Folkestone, Kent for
C. H. Boehringer Sohn, Ingelheim am Rhein.
Registered proprietors of the Trade Mark.


Pfizer
Σ
the deep spectrum antibiotic
Σ

Sigmamycin is a 2:1 combination of the broad-spectrum antibiotic tetracycline and the newly-discovered medium-spectrum antibiotic oleandomycin. Laboratory studies have clearly shown both in vitro *and* in vivo, *that this combination demonstrates synergism. The inhibitory concentrations required were significantly lower than those of the individual components added together. The advantages to be derived from this combination, which is the first of its kind, may profoundly affect the whole future pattern of antibiotic therapy.*

Σ

Σ

sigmamycin*

OLEANDOMYCIN TETRACYCLINE

depth in the broad spectrum

sigmamycin

is new: For the first time a broad-spectrum antibiotic has been combined with a medium-spectrum antibiotic to demonstrate true synergism.

is more effective: The synergistic combination of the two antibiotics adds depth to the broad spectrum of tetracycline, particularly against the common coccal infections.

is better tolerated: Matromycin, brand of oleandomycin, is an extremely well tolerated antibiotic and the synergistic action of the combination permits the use of smaller doses of tetracycline.

evokes a faster clinical response: The deep broad-spectrum activity of Sigmamycin ensures faster and more complete eradication of invading organisms. Control of infection is, therefore, more rapidly achieved.

delays bacterial resistance: Serial dilution tests have shown that the combination of antibiotics in Sigmamycin delays the emergence of resistant strains of bacteria. In general practice, it will be virtually impossible for resistance to appear.

THERAPEUTIC RANGE

Sigmamycin is a synergistic combination of tetracycline and oleandomycin. It has been shown to be highly effective against organisms sensitive to either or both of those drugs.[1] Sigmamycin therefore covers the broad-spectrum range of tetracycline but with enhanced activity against the staphylococcus and other Gram-positive organisms. Here, the presence of oleandomycin ensures a faster and more complete eradication of bacteria. The synergism of Sigmamycin and its deep spectrum offer excellent prospects of success against organisms already resistant to other chemotherapeutic agents.

INDICATIONS

The indications for Sigmamycin may be summarised under three headings:

(1) Infections due to organisms sensitive to one or both of its components.

(2) Infections due to unidentified organisms, when the maximum range of effectiveness, potency of action, and tolerance is required.

(3) Infections, identified or not, which have already shown resistance to other chemotherapeutic agents.

RECOMMENDED DOSAGE

Dosage with Sigmamycin varies with the type of infection, its severity, and the age and weight of the patient. Normal dosage for a moderate infection is 1 capsule every six hours. In severe infections this may be increased to 2 capsules every six hours, while in overwhelming infections a further increase may be needed.

AVAILABILITY

Sigmamycin is available in capsules containing 167 mg. tetracycline and 83 mg. oleandomycin, in bottles of 16 and 100 capsules.

1. *Tetracycline is effective against Gram-positive and Gram-negative bacteria, rickettsiae, spirochætes, large viruses, and the protozoa—Entemœba histolytica. Oleandomycin has shown activity both against Gram-positive organisms, including pneumococci, streptococci, and staphylococci, and against certain Gram-negative bacteria.*

Pfizer

WORLD'S LARGEST PRODUCER OF ANTIBIOTICS

PFIZER LTD · FOLKESTONE · KENT

* Trade Mark of Chas. Pfizer & Co., Inc

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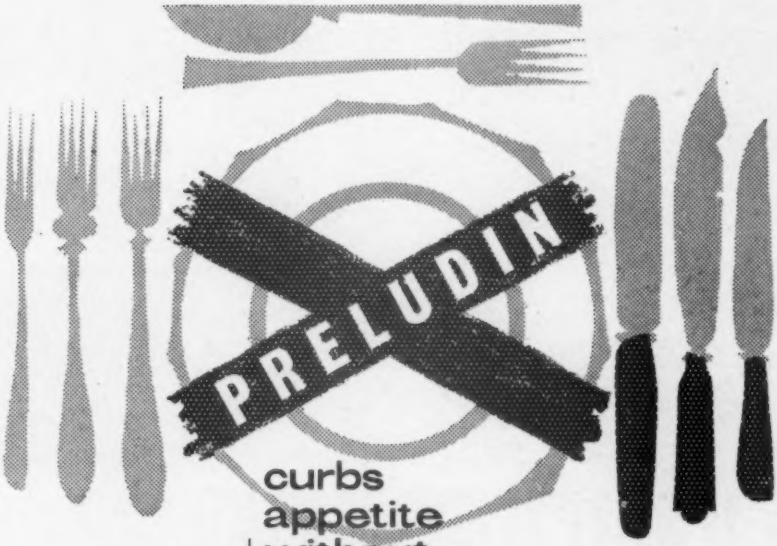


in cases of obesity

curbs appetite without affecting the heart

PRELUDIN is the doctor's powerful ally where weight reduction and adherence to diet are an essential part of the treatment. It is perfectly safe for cardiovascular conditions, and has no effect on blood pressure.
It is supplied in 25 mg. tablets, in tubes of 20 or bottles of 250.

PRELUDIN*

Brand of 2-phenyl-3-methyl-tetrahydro-1,4-oxazine-hydrochloride

The appetite controlling agent that does not affect the heart

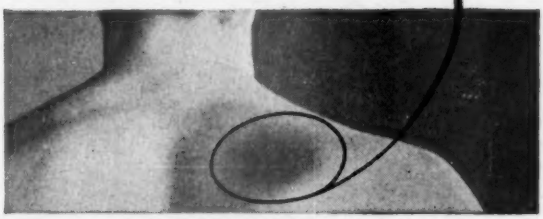
Manufactured and distributed in England by Pfizer Ltd., Folkestone, Kent, for

C. H. Boehringer Sohn, Ingelheim am Rhein

Registered proprietors of the Trade Mark *Regd. Trade Mark

Rubriment relieves pain in such conditions as muscular rheumatism, fibrositis, strains and sprains.

Some minutes after application the skin becomes flushed and there is a comforting feeling of warmth which persists for many hours.



RUBRIMENT

A new long-acting rubefacient—safe and effective

RUBRIMENT contains a new substance, the benzyl ester of nicotinic acid, which gives a long-lasting rubefacient effect. Experimental studies have shown that even after prolonged and repeated application no damage or irritation to the skin structure was caused.

Ten minutes after application there is a feeling of warmth and the area becomes flushed. This redness is due to the dilation of the small cutaneous blood-vessels. Clinical reports have been received of the efficacy of Rubriment for relief in such conditions as muscular rheumatism, lumbago, fibrositis, strains and sprains. The immediate and prolonged vasodilatory action of Rubriment also provides relief for unbroken chilblains.

Available in two forms Rubriment (2.5% nicotinic acid benzyl ester and 0.1% Capsicin) is available either as a cream or as a liniment, both of which are non-greasy.

The cream is rapidly absorbed and needs only gentle application. It is supplied in tubes of 20 g. (approx.). Basic price to N.H.S., 2/2d.

The liniment lends itself to massage, if this is required. It is supplied in bottles of 2 fl. ozs. (approx.). Basic price to N.H.S., 3/-.

Directions for use One application per day has been found to be effective for the majority of patients, though a fresh application may be made, if necessary, at more frequent intervals. ***Rubriment is not advertised to the public and can be prescribed on E.C.10.***

RUBRIMENT Horlicks Limited

PHARMACEUTICAL DIVISION SLOUGH BUCKINGHAMSHIRE

Metabolic Insufficiency

is a syndrome characterised by the co-existence of several signs and symptoms suggesting a state of metabolic dysfunction

In many patients suffering from Metabolic Insufficiency 'Cynomel' produces a positive improvement within a matter of days.
'Cynomel' should be administered discriminately. Before prescribing 'Cynomel' the physician should be fully conversant with the available literature.
In 5μg. and 25μg. (scored) tablets, both in containers of 100 and 1000.

Cynomel *L-triiodothyronine*

the new treatment for Metabolic Insufficiency

an SKF preparation 'Cynomel' is a trade mark

Smith Kline & French

CMP126 represented by Menley & James, Limited

B-PAS WANDER

PRODUCTS

These are now in unrestricted supply to provide the significant advantages of the newest clinically proven modification of PAS, i.e. B-PAS (4-Benzoylamino-2-hydroxybenzoic acid).

Extensive published reports based on the criteria of bacteriostatic levels, tolerability and clinical results show that B-PAS (Wander), first introduced by our Research Laboratories in 1948, is a major contribution to tuberculotherapy.

Calcium B-PAS (Wander) is virtually insoluble; hence its slower absorption and excretion, and ability to provide high blood levels of extended duration, but with relatively low dosage. In contra-distinction to other forms of PAS, B-PAS (Wander) is entirely free from unpleasant taste. It is thus acceptable to patients in easily taken powder form, as well as in cachets if preferred. The powder form is supplied in convenient single-dose envelopes, or in bulk in any quantity.

PACKS—Powder: Tins of 150 and 500 x 3.5 g. envelopes.
Cachets: ,, ,, 80 and 400 x 1.0 g.
Sodium B-PAS (Wander) also available in 1.5 g. Cachets.

'B-PASINAH' WANDER

combined B-PAS and Isoniazid (INAH)

For concurrent B-PAS (Wander) and INAH, this product is formulated so that 3 Powders daily provide 10.5 g. of Calcium B-PAS (Wander) plus 262.5 mg. of INAH. Also available as Cachets of 1 g. plus 25 mg. respectively.

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THE PRACTITIONER

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THE MONTH

The Symposium

In 1950 we published a symposium on 'Favourite Prescriptions'. This proved so popular that it was republished in booklet form. The continuing demand for this booklet indicates that it met a real demand among practitioners both at home and abroad. We have therefore decided to publish another symposium on the subject, but one designed on entirely different lines. The first symposium was based upon a classification of drugs according to the system of the body which was at fault. The rapid advance in therapeutics has made this approach less effective, and we have therefore planned the present symposium according to the action of the drug. Antibiotics and sulphonamides are effective, no matter which system of the body is involved, whilst analgesics are as effective for the relief of the pain of 'rheumatism' as of that due to vascular occlusion.

The art of prescribing has indeed changed since the days of our grandfathers. Some would even say that it is no longer an 'art', but a 'science'. This is as unjustified as the attempt to describe the 'practice of medicine' in the terms of 'clinical science'. It is abundantly clear from our symposium that prescribing is as much an art as ever, but an art which is dependent not only upon a sound knowledge of the properties, dosage and side-effects of drugs, but also upon the reaction of the individual patient. It is not only in the realm of nutrition that one man's food may be another man's poison. The drug which suits one patient may be either useless, or worse than useless, in another. In other words, the practitioner must still study the individual idiosyncrasies of his patients. Only when he knows these, as well as the properties of his drugs, will he be able to ensure that his patients are receiving the best possible treatment.

General Practice 1957

The medical profession, and particularly general practitioners, are entering the New Year in a mood of profound pessimism. With a unanimity, which even the most hidebound of lay bureaucrats must find impressive, the President of the British Medical Association, the President of the College of General Practitioners, and the Chairman of the Fellowship for Freedom in Medicine have expressed 'fear for the future of medicine and especially of general practice' unless, in the words of the President of the British Medical Association, action is taken, and quickly, 'to enlarge the area of freedom and dignity in medicine which still exists within the framework of the National Health Service'. As Dr. Grant, the new President of the College of General Practitioners, points out in the James Mackenzie Lecture, which

we publish this month (p. 85), 'both in general practice and in the consultant ranks . . . a feeling of frustration, disappointment, unhappiness and even despondency is to be found'. If this is indeed the state of affairs, where does the fault lie and what, if anything, can be done to cure it?

There can be little doubt that the crux of the problem is the National Health Service in its present form. The concept of such a Service may be magnificent but, to quote Dr. Grant again, 'each year since its inception more money is poured out on the Health Service and each year more money is expended in sickness benefit and each year more working hours are lost through illness'. There is obviously something very far wrong with a 'health' service which produces this result, and yet the Minister of Health does little more than keep on nagging doctors about their methods of prescribing, and virtually sabotaging the pharmaceutical industry's magnificent contribution to the nation's export drive. Radical action is clearly called for, and it is interesting to note the increasing emphasis that is being laid upon the separation of the Health Service from the political sphere. More and more of the profession are coming round to Dr. Grant's point of view that 'so long as the health of the nation is used as a vote-catching instrument by the politicians, so long we, as doctors, must feel that we are mere pawns in the game of political chess'. Statesmanship will be called for if such a radical change in the Health Service is to be considered, and statesmanship today seems to be as rare a commodity as the golden sovereign. Unless action is taken quickly professional freedom will be a thing of the past, and the country will find itself with a whole-time medical service in which, in Dr. Grant's words, 'doctors would become a body of expert officials who might or might not be able to maintain their high standard of ethical conduct'. Professional freedom is our birthright. It is nothing less than that which is at stake. Unless the profession pulls itself together and concentrates upon the essentials, and not the frills, we shall all be salaried civil servants, working a forty-hour, five-day week, and accepting our orders from a layman appointed according to the political propensity of the party in power.

Ambulance Driving

LAST month (p. lxxxviii) our Motoring Correspondent drew attention to what he euphemistically described as the 'selfish' driving of ambulance drivers. This was more accurately described as 'lack of safety driving' by Mr. William Gissane, the clinical director of the Birmingham Accident Hospital, in his article on 'The prevention of road accidents' which we published some three years ago (*The Practitioner*, 1954, **172**, 620). How widespread this type of driving is, we are not aware. So far as London is concerned, however, there can be little doubt that ambulance drivers as a whole are not maintaining the high standard of courtesy and safe driving which the public is entitled to expect from them. The discordant note of their 'bells' as they race through the traffic, shooting in and out, often on the wrong

side of the road, is neither necessary, courteous nor safe. Our Motoring Correspondent is by no means the only person who 'would suffer nervous shock' if driven in an ambulance in this manner.

No-one questions the right of an ambulance to be given a certain amount of priority, and there is no motorist who would not give way to one if necessary. But how often is such speeding necessary? As Mr. Gissane pointed out, 'a few minutes lost in arriving at hospital with a patient is seldom vital; a collision by neglecting elementary road safety can be, and in my experience has been, fatal to a patient in transport'. The good ambulance driver is among the best drivers in the country, but there are too many who appear to abuse the privilege rightly granted to them by other motorists. We trust that this matter will receive the careful attention of those responsible for the ambulance services of the country, and that they will ensure that their drivers obey the dictum of Mr. Gissane: 'The rule of safety on the road should be observed by all road vehicles, and the more official the vehicle the safer should be the driver's behaviour. Official vehicles would do well to follow the example of safety driving set by the Police service'.

U.S. and U.K.

REALIZING the need to maintain the close cooperation between the medical services of this country and those of the United States of America, which developed during the 1939-45 War, we instituted in 1945 a policy of inviting distinguished American doctors to contribute to our symposia. In 1948, in order to develop and coordinate this scheme, we appointed a Consultant Editor in the United States. As a further development of this policy we have now arranged with the *New England Journal of Medicine* to introduce an arrangement whereby subscribers to each journal may obtain the other at a reduced rate. Full details of this scheme will be found on p. 140 of this issue.

The *New England Journal of Medicine*, which was established in 1828 under the title of the *Boston Medical and Surgical Journal*, is internationally recognized as one of the leading medical journals in the United States. Its policy is very much like that of *The Practitioner*, the aim being to provide clinicians, whether in general or consulting practice, with authoritative reviews of current practice in all branches of medicine. Its original articles are drawn from all parts of the United States and are representative of the best work being done over there. To many readers on this side of the Atlantic it is probably best known for its 'Case Records of the Massachusetts General Hospital', which still proudly bear the subtitle 'Founded by Richard C. Cabot', and which have now practically reached their 42,500th case. We feel therefore that our two journals are essentially complementary to each other, in providing a balanced review of medical practice in our two countries. We trust that, in the characteristically well-chosen editorial words of the *New England Journal of Medicine*, this 'happily independent symbiotic relation, with science and social consciousness transcending political considerations' will commend itself to our readers.

Equipping the Surgery

In 1955, we published a series of six articles on 'The Doctor's Surgery'. These dealt with the problem of planning and building a surgery, and covered subjects such as ventilation, lighting, heating, and furnishing. Of equal importance to the man in practice is the subject of what equipment he should provide himself with. We are therefore introducing this month a series of articles entitled 'Equipping The Surgery'. In these, experts will give advice on the instruments and apparatus which the practitioner should possess in order to provide an efficient service for his patients. The first article, which will be found on p. 115, deals with 'Instruments and sutures', and the second will be devoted to 'Dressings and antiseptics'. These two subjects have been chosen as the introductory articles because of the increasing emphasis being laid upon the importance of the general practitioner doing his own minor surgery instead of referring the patient to hospital.

Whilst this series will be of primary interest to the young practitioner setting up in practice, we trust that our older readers will also find it of interest in helping them to ensure that their equipment is up to date and in accordance with the best standards of current practice. Our contributors will be pleased to deal with any queries from readers arising out of their articles. These should be addressed in the first instance to The Editor, *The Practitioner*, 5 Bentinck Street, London, W.1.

Travel Notes

The doctor is probably the one member of the community who can never depend upon being left at peace in his own house. So long as he is there he is expected to obey the imperious summons of the telephone or the importunate patient on his doorstep. Even a holiday in his own country may not give him complete relief from the calls of practice. This is probably one of the reasons why doctors are tending more and more to holiday abroad. Once he has crossed the English Channel his absence is likely to be accepted. To travel these days is becoming increasingly easy, but to travel discriminately increasingly difficult.

It is to help the discriminating doctor in the choice of his holiday resort that we are introducing this month a new series of articles entitled 'Travel Notes'. In these, the first of which will be found on p. A97, Miss Penelope Turing, herself an experienced traveller and a well-known writer on the subject, will provide a monthly commentary on holidays and where to spend them. As in the case of our 'Motoring Notes', which have proved such a popular feature, Miss Turing will be pleased to answer queries from our readers, and both she and we will welcome suggestions for subjects with which she can deal. The series will include occasional articles dealing with the problem of where doctors can recommend their convalescing patients to go for suitable holidays. All queries and suggestions should be addressed to: Miss Penelope Turing, *The Practitioner*, 5 Bentinck Street, London, W.1.

ANTIBIOTICS

By E. J. WAYNE, M.D., F.R.C.P., F.R.C.P.Ed.
Regius Professor of Practice of Medicine, University of Glasgow

It is comparatively easy to know when to give a symptomatic remedy such as an analgesic or hypnotic; it is, however, often difficult to select the appropriate antibiotic in infections.

SOME BASIC PRINCIPLES

In the first place, accurate diagnosis is essential. The presence of pyrexia is not in itself conclusive evidence of infection and even when other symptoms and signs show that infection is present it does not necessarily follow that antibacterial drugs should be used in treatment. There are many infections, including almost all the virus infections, for which no specific remedies are known. There are others such as a single boil in which the possibility of sensitizing the patient is more important than the doubtful benefit which an antibiotic might produce. Thus, before deciding to use an antibiotic the prescriber should be fully satisfied that he knows the nature of the condition he is treating and that it is likely to respond to specific therapy. It is a great advantage if the causative organism can be determined and if possible cultured and isolated. This enables treatment to be put on a rational basis since the bacteriologist can determine the sensitivity of the organisms to different antibiotics. Unfortunately this is possible only in certain types of infection: e.g. those of the respiratory system, the genito-urinary tract and in superficial pyogenic infections. Treatment, however, should not be delayed until the results of laboratory investigations are available but samples for examination should be sent before antibiotics are given. In many diseases, such as otitis media, it is necessary to assume that the organism is the one commonly responsible for the condition and to select the appropriate remedy using the patient's response as an indication of the sensitivity of the infecting organisms.

When the prescriber has decided on the use of an antibacterial drug he must next consider whether he should use a member of the sulphonamide group or an antibiotic. The present-day tendency is probably towards using the 'broad-spectrum' antibiotics too freely while neglecting the sulphonamides which are less likely to give rise to gastro-intestinal side-effects.

PENICILLIN

This is by far the safest and the cheapest antibiotic. It is virtually non-toxic except for allergic reactions, although procaine penicillin has given rise to collapse as the result of accidental intravenous injection. It is always wise to ask a patient if he is penicillin-sensitive before giving an injection of the drug. The action of penicillin is not greatly affected by the number

of organisms present and is maintained even in the presence of serum and pus. Its main disadvantage is its rather limited 'spectrum' and the fact that it is most effectively administered by injection. A large number of preparations is available but comparatively few are necessary in the treatment of infections where the drug is indicated. Even among organisms sensitive to penicillin there are great differences in sensitivity; some strains of hæmolytic streptococci may be inhibited by as little as 0.003 unit per ml. whilst the average *Streptococcus viridans* isolated from cases of subacute bacterial endocarditis requires concentrations of 0.12 unit per ml. When organisms are relatively inaccessible, as in boils or walled-off collections of pus, high blood levels such as are found after large doses of soluble penicillin may aid penetration into the relatively avascular tissues.

In most conditions, however, it is sufficient to have a lower blood level which remains bacteriostatic during the whole of the period of therapy. A single daily injection of procaine penicillin achieves this result. It is extremely difficult to devise observations in man which will show conclusively whether continuous or intermittent bacteriostatic levels in the blood are more effective. It should be remembered that in the days when penicillin was scarce striking clinical improvement was often obtained with doses as low as 80,000 units a day. With the large doses given today it is not surprising that failure can rarely be attributed to the type of preparations used. The following are the more important types of penicillin.

Benzylpenicillin is supplied as the sodium or potassium salt and is usually known as soluble penicillin. It is given by intramuscular injection in a dose of 250,000 to 1 million units two to four times daily. These doses, which at first sight appear to be very large, are in fact comparable to those of other antibiotics since 1 million units of penicillin is an alternative term for 600 milligrammes of solid benzylpenicillin. In most infections a dose of 500,000 units twice a day or even a single injection of 1 million units a day will give satisfactory clinical results although they will not always give continuous bacteriostatic blood levels.

Penicillin can be given *by mouth* but the proportion absorbed varies greatly. Doses of 300,000 to 600,000 units six-hourly, usually but not invariably, give blood levels adequate for the treatment of conditions due to sensitive organisms. It is always advisable to give the first dose by injection. Side-effects such as diarrhœa, sore tongue and angular stomatitis may occur.

Procaine benzylpenicillin is relatively insoluble and a single daily intramuscular injection of 600,000 units will always give a bacteriostatic blood level for twenty-four hours.

Benzathine penicillin is a relatively insoluble derivative of penicillin which is more stable in the presence of moisture and has a less bitter flavour. It is doubtful if it produces higher blood levels than soluble penicillin when given orally in comparable doses. If it is injected intramuscularly it gives low but very prolonged blood levels.

Phenoxymethylpenicillin (*Penicillin V*) is also relatively stable and less

bitter than soluble penicillin. It is given orally and produces higher blood levels than other forms of oral penicillin in comparable doses. It is prescribed by weight and the dose is of the order of 120 to 240 mg. (equivalent to 200,000 to 400,000 units of soluble penicillin) four-hourly.

Choice of preparation.—The oral preparations have the advantage of ease of administration and are especially valuable in infants and young children. Phenoxymethylpenicillin will probably eventually replace the other preparations. It is usually preferable to give penicillin by injection and in the case of severely ill patients, or when the nature of the infecting organisms is uncertain, at least the first injection should contain some soluble penicillin. Many preparations exist containing two or three of the injectable forms of penicillin and may be of value in some circumstances. If there is any reason to suspect that the organisms are relatively insensitive or are walled off it is better to use frequent injections of soluble penicillin.

STREPTOMYCIN

The main use of this antibiotic is in the treatment of tuberculosis. It is, however, active against many organisms which are not penicillin sensitive including many gram-negative organisms. Its great defect is its tendency to produce resistant strains and this may occur with great rapidity. In short-term use the only side-effects likely to occur are those due to allergy and albuminuria. To produce systemic effects streptomycin must be injected intramuscularly and in mixed infections it may be desirable to give penicillin at the same time.

THE TETRACYCLINES

There are three members of this family: *tetracycline* itself ('achromycin', 'ilotycin'), and two derivatives—*chlortetracycline* ('aureomycin') and *oxytetracycline* ('terramycin'). The range of their antibacterial activity is essentially the same. They are all broad-spectrum antibiotics and are effective against a wide range of gram-positive as well as gram-negative bacteria and against a few of the larger viruses. Their chief place is in the treatment of infections not responding to sulphonamides or to penicillin. Although they have the advantage of the oral route of administration, they are particularly liable to cause vomiting and diarrhœa and to lead to a sore tongue and monilial infections of the mouth, anus or vagina. It is wise to give supplementary vitamin B complex if tetracyclines are given for more than a few days. A particularly dangerous complication is 'superinfection': that is to say, the bowel may be invaded by staphylococci resistant to all chemotherapeutic agents. A cholera-like syndrome then supervenes and is often fatal. Superinfection by monilia may occur but is less serious. There is some evidence that tetracycline is less likely to cause alimentary side-effects than its derivatives.

The daily dose should not exceed 2 g. and it is wise to try the effects of 250 mg. six-hourly in the first instance and to regard this as the usual standard dose.

OTHER ANTIBIOTICS

Chloramphenicol.—The major disadvantage of this broad-spectrum antibiotic is its liability to cause blood dyscrasias, especially a fatal aplastic anæmia. It should be used in small doses and for short periods and in no case should the total dose exceed 26 g. in an adult. It may be justifiably administered in enteric fever, influenzal meningitis and in serious infections due to staphylococci insensitive to other antibiotics.

Erythromycin has a range of activity similar to that of penicillin. It has few toxic side-effects but bacteria develop resistance to it rather rapidly. Its use is best reserved for the treatment of staphylococcal infections proved by laboratory tests to be insensitive to other antibiotics. It may also be used for the treatment of 'diphtheria carriers'. It is given orally in doses of up to 2 g. a day in adults.

Spiramycin (*'rovamycin'*), an antibiotic not yet fully investigated, may have a use in staphylococcal infections resistant to other antibiotics.

Novobiocin (*'albamycin'*), a recently introduced antibiotic, is active against various gram-positive organisms, including staphylococci. High blood levels are obtained and maintained after oral administration. Sensitization may occur and leucopenia has been reported. It may have a place in the treatment of staphylococcal infections resistant to other antibiotics.

Polymyxin B is the antibiotic of choice in infections due to *Ps. pyocyanea.* A suitable dose is 200,000 units six-hourly by intramuscular injection.

Bacitracin and neomycin are poorly absorbed when given by mouth and may be used in the dysenteries and to produce relative sterility in the bowel before intestinal operations. Either may be applied locally to infected skin.

COMBINATIONS OF ANTIBIOTICS

Penicillin and streptomycin, which are bactericidal when present in sufficient concentration, may be given together and may potentiate one another. Most of the other antibiotics in common use are bacteriostatic and in combination give simple additive effects. There is some evidence that it is inadvisable to give a bactericidal and a bacteriostatic antibiotic simultaneously since the net result may be less than when either is given alone.

Recommendations for the treatment of different conditions will now be given. They represent the author's own point of view. A comparison with the suggestions made by Valentine (1956) however, will, reveal little fundamental disagreement. This is perhaps not remarkable since the use of antibiotics rests on sound theoretical bases.

DISEASES OF THE RESPIRATORY TRACT

Acute tonsillitis and *scarlet fever* are best treated with penicillin unless the attack is a mild one. The drug can be given orally as phenoxymethylpenicillin (Penicillin V), 120 mg. four-hourly. A less satisfactory alternative is soluble penicillin, 600,000 units six-hourly by mouth. In each case about two-thirds of the adult dose suffices for children. More certain effects are

obtained if procaine penicillin is given by injection and in severe cases the first dose at least should be given by this route. A suitable dose would be 300,000 units daily. Usually treatment need not be continued for more than four days. A recent well-controlled trial has shown that both streptococcal and non-streptococcal sore throats improve more rapidly when treated by oral penicillin than when no antibiotic is used (Chapple *et al.*, 1956). The sucking of lozenges or tablets containing penicillin is valueless and may be harmful.

Acute sinusitis and *acute otitis media* should be treated in the same way as acute tonsillitis. Because of the danger of subsequent deafness in otitis media it is advisable to give an initial injection of soluble penicillin or preferably one of the mixtures of soluble and procaine penicillin: e.g. injection of procaine benzylpenicillin and benzylpenicillin B.P.

Acute tracheitis and *bronchitis.*—Antibiotics need not be used except in infants, the elderly, and those with significant pyrexia in whom there is probably patchy consolidation. Penicillin should be given as in pneumococcal pneumonia (see below). If there is no response after forty-eight hours, tetracycline should be given in a dose of 250 mg. six-hourly. In spite of its greater liability to produce side-effects it has the advantage over penicillin of activity against *H. influenzæ* and a wider range of strains of staphylococci.

Bronchiectasis.—Postural drainage should be instituted. The sputum should be cultured before and during treatment and the results should be used as a guide in the choice of an appropriate antibiotic. Soluble penicillin by injection in large doses, e.g. 500,000 units twice daily, almost always gives some improvement but there is a tendency for the number of gram-negative organisms in the sputum to increase. Streptomycin, 0.5 g. twice daily, may be given in addition for not more than seven days. Tetracycline, 250 mg. six-hourly, may be used with advantage in some patients. The side-effects and the expense of the treatment with tetracycline must be weighed against the chances of improvement which are in any case only temporary.

Chronic bronchitis in exacerbations or when the sputum is purulent should be treated in the same way as bronchiectasis.

Pneumonia.—Both specific and aspiration pneumonias are treated similarly and it is a great advantage to know the nature of the infecting organisms. Treatment must not be postponed, however, until the results are available. The great majority of pneumonias, probably more than 90 per cent., respond to penicillin therapy. The pneumococcus is sensitive to penicillin and for the average case 500,000 units of soluble penicillin every twelve hours, or 300,000 units of procaine penicillin once a day, are adequate doses. If the latter preparation is used, the first dose should contain some soluble penicillin: i.e. the official fortified injection of procaine penicillin. In patients who are not very ill and in children it may be permissible to use oral penicillin, preferably as phenoxymethylpenicillin, after the first injection. If there is no response after forty-eight hours and no bacteriological information is available, tetracycline, 1 g. daily, may be used. If a bacteriological

report shows penicillin-resistant pathogenic organisms, e.g. *Staph. aureus* or *H. influenzæ*, it will usually contain information suggesting the most suitable alternative antibiotic: Friedländer's bacillus, for instance, usually responds well to streptomycin in full doses.

Virus pneumonias of the 'primary atypical pneumonia' type are rare in this country and should be diagnosed infrequently. Tetracycline is the appropriate remedy but it should be remembered that most cases are actually examples of 'benign aspiration pneumonia'.

Pertussis responds to the tetracyclines if they are given in the early stages of the disease. Since whooping-cough is a serious condition in infancy and in debilitated children tetracycline is recommended in these cases. The dose is 35 mg. per kg. body weight and it should be given for at least a week. Antibiotic treatment is not necessary in mild cases or in those seen after symptoms have been present for more than a week.

STAPHYLOCOCCAL INFECTIONS

These are the main problem of chemotherapy today since strains of staphylococci resistant to penicillin are becoming increasingly common, especially in hospital practice. Fortunately, many of the strains are susceptible to other antibiotics but some have been isolated which are unaffected by any at present available. If the staphylococcus can be isolated its sensitivity to different antibiotics should be estimated and the appropriate remedy chosen. While waiting for this information soluble penicillin should be given in a dose of at least 250,000 units six-hourly. If there is no response after forty-eight hours, and it has not proved possible to obtain the sensitivity of the organism, erythromycin should be tried in a dose of 0.5 g. six-hourly. If there is still no response chloramphenicol is the next substance to use and finally one of the tetracyclines. Whichever antibiotic is used, treatment must continue for long periods: e.g. two to three weeks. In staphylococcal enteritis due to superinfection the most appropriate antibiotic is erythromycin—at least until the results of sensitivity tests are available.

MENINGITIS

Lumbar puncture should be performed as soon as possible and the responsible organism should be isolated and its sensitivity determined. Since treatment must be started before this can be done it is usual to give both a sulphonamide, either sulphadimidine or sulphadiazine by mouth, and penicillin intramuscularly. If the cerebrospinal fluid is obviously purulent when the diagnostic puncture is carried out, 10,000 units of soluble penicillin may be injected intrathecally straight away. Large doses of penicillin are advisable in treating meningitis: e.g. 1 million units of soluble penicillin three times a day. If the organism isolated is a meningococcus, sulphonamides are of more value than penicillin. In other types of meningitis guidance will be obtained from the bacteriological report of sensitivity. Pneumococcal meningitis is best treated with intrathecal penicillin: 10,000

units daily plus 1 million units of soluble penicillin intramuscularly with or without sulphadimidine by mouth. In meningitis due to *H. influenzæ* chloramphenicol is usually the best drug: 100 mg. per kg. body weight.

URINARY-TRACT INFECTIONS

Acute pyelonephritis (pyelitis) is commonly due to infections by gram-negative organisms, especially *E. coli*, and responds well to sulphonamides and alkalis. If response is not rapid and complete, a sensitivity test should be carried out after culture. If the patient is vomiting it may in any case be necessary to give streptomycin or a combination of streptomycin and penicillin by injection. Some strains of *E. coli* are only relatively insensitive to penicillin and may be affected by the high concentration which this antibiotic achieves in the urine. In patients with severe constitutional disturbances it is justifiable to use a broad-spectrum antibiotic, e.g. tetracycline, from the beginning of the illness since the infection responds more rapidly to an antibiotic than to a sulphonamide. A course of any antibiotic may often with advantage be followed by several weeks' treatment with small doses of a sulphonamide: e.g. 0.5 g. sulphadimidine twice daily.

In relapsing and chronic cases there is usually some abnormality of the urinary tract and full investigation is necessary. In the palliative treatment of chronic infections where the cause cannot be removed *B. proteus* is a commonly isolated organism. Such infections are best treated by nitrofurantoin ('furadantin'). Infections by *Ps. pyocyanea* may respond to polymyxin B in a dose of 20,000 units per kg. body weight a day.

SUBACUTE BACTERIAL ENDOCARDITIS

By far the commonest causative organism is the *Streptococcus viridans*. It is always easier to treat the condition satisfactorily if the organism has been isolated and its sensitivity determined. The standard course of treatment is 2 million units of soluble penicillin a day given intramuscularly in divided doses for six weeks. Penicillin, 10 million units daily, combined with streptomycin, 2 g. daily, for a fortnight has recently been claimed as an adequate course of therapy (Geraci, 1955), but is not recommended until more experience has been gained. In exceptional cases erythromycin or tetracycline may be used. Treatment of infected teeth or tonsils in patients with a valvular or congenital heart lesion should always be conducted under penicillin cover: e.g. 300,000 units of procaine penicillin for three days, beginning the day before the operation.

ALIMENTARY INFECTIONS

Enteric fever.—Chloramphenicol is the antibiotic of choice and should be given in a dose of 2 g. a day until the fever has disappeared and then in a dose of 1 g. a day for seven to ten days. A second course may be necessary for patients in relapse. The drug is useless in the chronic carrier state.

Bacillary dysentery.—A sulphonamide may be used or oral streptomycin,

0.5 g. twice daily, but in a clinical trial tetracycline, 500 mg. six-hourly for seven days, was found to be more effective than these substances, at least in Sonne dysentery (Abbott and Parry, 1955).

Salmonella infections.—Infections with this group of organisms do not respond well to antibiotics. Chloramphenicol may be given in cases of Salmonella septicæmia but its value is doubtful.

Peritonitis may be treated by soluble penicillin, 500,000 units twice a day, along with streptomycin, 1 g. twice a day, for seven days. This is the preferable course if the patient is vomiting. Alternatively, tetracycline or oxytetracycline may be given orally in a dose of 0.5 g. four times daily for a week.

Acute cholecystitis.—Penicillin and streptomycin are often used as in peritonitis. Oxytetracycline may have advantages over other antibiotics but when the cystic duct is obstructed chemotherapeutic agents do not usually appear in the gall-bladder lumen. Doses of 500 mg. are advised (Zaslow and Rosenthal, 1954).

VENEREAL DISEASES

Syphilis is treated with procaine penicillin and the usual standard dose consists of 600,000 units daily for ten days. Most venereologists prefer the preparation in oil containing 2 per cent. aluminium stearate (PAM). In early cases a single injection of 2.4 million units of this preparation or of benzathine penicillin may give a cure and can be given when there is little chance of the patient returning for further treatment.

Gonorrhœa is usually cured by a single dose of 300,000 units of procaine penicillin intramuscularly.

Lymphogranuloma venereum and *granuloma venereum* respond to the tetracyclines and the latter to streptomycin as well.

For a full review of the present status of antibiotics in venereology, the reader is referred to the recent article by King (1956).

RELATIVELY RARE DISEASES

Rickettsial infections respond to tetracycline or chloramphenicol. Tetracycline in a dose of 250 mg. every six hours for four days is usually adequate.

Psittacosis may be treated similarly.

Brucellosis may be treated with tetracycline, 2 g. a day for at least a fortnight. There is evidence that a course of streptomycin or dihydrostreptomycin, 2 g. a day over the same period, diminishes the relapse rate.

Weil's disease is best treated by soluble penicillin, 2 million units a day, or tetracycline, 2 g. a day in divided doses, but the evidence that they cure the disease is not convincing.

Anthrax and *actinomycosis* are best treated with full doses of penicillin.

THE PROPHYLACTIC USE OF ANTIBIOTICS

There is some difference of opinion about prophylaxis by antibiotics (Mitman, 1955; Garrod, 1955). Penicillin is the only one which can be given over long periods without producing side-effects and is the most

suitable, even in short-term use. The chief drawback even of penicillin is the danger of sensitizing the patient so that if he later develops a severe infection it may be impossible to treat this with the same drug. It is legitimate to use penicillin prophylactically in cases in which there is a danger of subacute bacterial endocarditis after minor operations such as teeth extraction. In minor surgery penicillin should not be used as an alternative to adequate surgical technique. In major surgery, e.g. thoracic surgery, penicillin is usually given on the day of operation and for several days subsequently. Prophylactic antibiotic administration is never necessary in normal labour but may be desirable after manual interference. In the specific fevers due to virus infections, e.g. measles, penicillin may be given by mouth to prevent respiratory complications. For the prophylaxis of acute rheumatism penicillin by mouth in a dose of 250,000 units twice a day or benzathine penicillin (22,000 units per kg.) intramuscularly weekly may be used.

CONCLUSION

It has been estimated by Jawetz (1954) that 'only 1 to 5 per cent. of antimicrobial drugs are administered on a proper clinical indication'. Their indiscriminate use is probably less in this country than in the United States, but even here far too many patients are still exposed to the unpleasant side-effects and occasional dangers to which all antibiotics may give rise. Moreover, the community as a whole is rendered a disservice when micro-organisms are rendered resistant by widespread and unnecessary administration. It is therefore desirable to end these notes by pointing out the common mistakes which are made in prescribing these powerful remedies.

In the first place, antibiotics are far too often prescribed for patients who do not require them. In general it is true that antibiotics are rarely needed in apyrexial patients and if a patient is ill enough to receive an antibiotic he is usually ill enough to be in bed. Broad-spectrum antibiotics with their potential unpleasant side-effects are often used instead of penicillin when penicillin would be a better choice. Treatment is far too often continued although there is no clinical response and when there is a response an antibiotic is often given over too long a period: a mistake which is especially liable to occur in hospital practice.

In general it can be said that the physician who shows some restraint and who makes penicillin his first choice is likely to do more good and is certain to do less harm than he who prescribes antibiotics indiscriminately.

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THE SULPHONAMIDES

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THE introduction of the sulphonamides into therapeutics marked the beginning of direct attack upon infections. Since then the antibiotics have arrived upon the scene in increasing number and the difficulty now is to remember which one is effective against any particular organism. The sulphonamides were widely used at first with varying results, which is not surprising in view of the different sensitivity of various organisms. In some infections the antibiotics have superseded the sulphonamides but the latter have a definite part to play in therapeutics, and if used in the right case in adequate dosage the results are gratifying.

MODE OF ACTION

The sulphonamides are bacteriostatic. They inhibit multiplication of sensitive organisms, probably by blocking enzyme systems. This inhibition allows the natural defence mechanisms of the body to deal with the existing infection without being overwhelmed. This applies to all sulphonamides and the difference in action of various preparations is one of degree. For effective treatment therefore it is essential to ensure an adequate concentration of sulphonamide at the site of infection for a sufficient length of time.

ABSORPTION, DIFFUSION AND EXCRETION

The rate of absorption and excretion of different preparations varies widely and this is of importance when considering which preparation to use in a particular case. Diffusion into the cerebrospinal fluid and serous cavities is also variable and has to be considered in infections at these sites.

The ideal sulphonamide for systemic use would be one which was rapidly absorbed, diffused readily, and which was slowly excreted. Table 1 shows

Preparation	Absorption	Diffusion	Excretion
Sulphathiazole	Rapid	Poor	Rapid
Sulphadiazine	Rather slow	Good	Rather slow
Sulphamerazine	Moderate	Good	Slow
Sulphadimidine ('sulphamezathine')	Rapid	Good	Rapid
Sulphamethizole ('urolucosil')	Rapid	—	Rapid
Sulphafurazole ('gantrisin')	Rapid	Moderate	Rapid
Succinylsulphathiazole	Slow	—	—
Phthalylsulphathiazole	Slow	—	—

TABLE 1.—The rates of absorption, diffusion and excretion of the more commonly used sulphonamides.

the characteristics of some of the preparations in common use. Acetylization inactivates sulphonamides and there is considerable variation in the degree to which each compound becomes acetylated. Solubility also differs, and

the more soluble sulphonamides are less likely to cause crystalluria.

SENSITIVITY OF ORGANISMS

Most strains of β-hæmolytic streptococci, pneumococci, and meningococci are sensitive. Staphylococci vary in their degree of sensitivity, and penicillin is the treatment of choice in infections due to this organism. Gonococci may be sensitive but sulphonamide resistance has appeared in many strains. *E. coli*, some Salmonellæ and the dysentery bacilli are usually sensitive, but most other pathogenic bacilli are relatively insensitive and infections caused by them are best treated with antibiotics.

The success or failure of sulphonamide therapy will depend largely upon the sensitivity of the infecting organism, provided the dosage and choice of preparation are correct. It is often necessary to treat acute infections before the organism has been isolated by the laboratory, if indeed this is practicable, but it is usually possible to achieve from the clinical picture a shrewd idea as to the probable organism. It is reasonable to start sulphonamide therapy in suitable cases while awaiting the bacteriological findings.

IN RESPIRATORY DISEASES

Lobar pneumonia is usually due to the pneumococcus and can be treated successfully with sulphonamides. Sulphadimidine is suitable and of low toxicity. An initial loading dose of 2 g. should be followed by 1 g. four-hourly for six to seven days. Failure to respond rapidly suggests one of three things: a faulty diagnosis, the development of an empyema, or a resistant organism. *Broncho-pneumonia* can be successfully treated when due to sensitive organisms. Sulphonamides can be used as in the case of lobar pneumonia, together with a suitable antibiotic. If used alone, failure to respond rapidly should indicate a change of treatment. Sulphonamides are not the treatment of choice in *empyema* or *lung abscess*, but there is some evidence of a synergistic effect when used together with penicillin.

Sulphonamides have no effect on *acute bronchitis*, but it is often difficult to tell where bronchitis ends and broncho-pneumonia begins. It is reasonable to use sulphonamides in severe bronchitis when the onset of broncho-pneumonia would be a serious event. In such cases full dosage should always be used, as for pneumonia. Sulphonamides have been administered to patients with *chronic bronchitis* throughout the winter in small dosage with the object of warding off episodes of broncho-pneumonia. The value of this prophylaxis is doubtful. Sulphadiazine or sulphamerazine are suitable preparations, in doses of 0.5 g. twice a day.

There is no real proof that sulphonamides are of any value in *upper respiratory infections* and, as treatment with these drugs is not entirely without risk, there seems little justification for their use.

IN SEPTICÆMIA

In these severe infections antibiotics are necessary and if sulphonamides

are used it must be in a secondary role. In subacute bacterial endocarditis the use of sulphonamides may mask the clinical picture and so delay diagnosis and the institution of correct antibiotic therapy.

Meningococcal septicæmia is an exception in that it responds well to sulphonamides; in fact this is probably the treatment of choice. It is characterized by bouts of fever, malaise, joint pains and petechiæ and by a purplish rash not unlike erythema nodosum. It may continue intermittently for months without meningitis developing, although this can occur at any stage. Treatment with sulphadimidine or sulphadiazine is dramatic. The loading dose should be 2 g. followed by 1 g. four-hourly for three days and then 1 g. six-hourly for three days.

IN MENINGITIS

The nature of the infecting organism is again the deciding factor. In meningococcal meningitis the sulphonamides are the treatment of choice and here the initial dose should be large enough to obtain an adequate concentration quickly. Sulphadimidine is effective, using a loading dose of 2 g. followed by 1 g. four-hourly for four or five days. If the response is satisfactory the dose can then be reduced to 1 g. six-hourly for two or three days.

If there is doubt about keeping up an adequate fluid intake, trisulphonamide tablets N.F. may be used. This is a mixture of sulphadiazine, sulphathiazole and sulphamerazine and is unlikely to cause crystalluria:—

Sulphadiazine	0.185 g.
Sulphathiazole	0.185 g.
Sulphamerazine	0.130 g.

Should the patient be unable to swallow, or the infection be severe, sulphadimidine sodium should be given parenterally. It may be given intravenously or intramuscularly in the same dosage as by mouth; 1 g. of sulphadimidine sodium is contained in 3 ml.

Meningitis due to other organisms is best treated with antibiotics although sulphonamides may be used with them.

IN URINARY DISEASES

Most infections of the urinary tract are due to *E. coli*, and most of these organisms are sensitive to the sulphonamides. The latter are therefore a potent weapon in the treatment of pyelitis and cystitis. The aim of treatment should be to maintain an adequate concentration of sulphonamide in the blood and in the urine, without undue risk of crystalluria. In any event, fluid intake should be at least five pints (3 litres) a day, and it is helpful to render the urine alkaline as this cuts down the risk of crystalluria and enhances sulphonamide action. The main action of sulphonamides is probably via the blood stream even in cystitis and especially in pyelitis which always means some degree of pyelonephritis. Trisulphonamide tablet N.F. is particularly suitable: a loading dose of 2 g. followed by 1 g. four-hourly for five days is

effective. The dose is often reduced to 1 g. six-hourly after forty-eight hours. Sulphamethizole ('urolucosil') is sometimes preferred: 0.2 g. six-hourly for six or seven days is sufficient. This preparation is highly soluble and of low toxicity, and it is inexpensive. It is unnecessary to render the urine alkaline as sulphamethizole is very soluble at pH 7. Sulphafurazole ('gantrisin'), 2 g., followed by 1 g. four-hourly, also has its advocates. It is highly soluble and alkalinization of the urine is not essential. Whichever drug is used the principles remain the same and in the right dosage the results will be satisfactory.

If the patient fails to respond or relapses, further investigation is essential. The organism may be insensitive or it may not be *E. coli*. There may be a calculus or an obstructive lesion of the urinary tract and these possibilities must always be considered. Where an indwelling catheter is necessary sulphonamides are useful in keeping infection in check. Sulphamethizole is satisfactory, 0.2 g. eight-hourly, and can be continued for long periods. This treatment can also be used when repeated infections of the urinary tract occur but only after full investigation has been carried out and complicating factors such as calculi have been dealt with.

IN GONOCOCCAL INFECTIONS

When first used for this purpose sulphonamides were dramatically effective but soon resistant strains of gonococci began to appear. Penicillin has now largely replaced sulphonamides in the treatment of gonorrhœa but has the disadvantage that it may mask a coexistent syphilitic infection.

Sulphonamides are effective in treating ophthalmia neonatorum whether gonococcal or not. Systemic treatment is essential and sulphadimidine is safe and effective in the total daily dosage of 0.3 g. per kg. body weight given four-hourly by mouth.

IN GASTRO-INTESTINAL DISEASE

Sulphonamides have been used extensively in the treatment of bacillary dysentery. They have been largely superseded by the antibiotics although they were reasonably effective in the form and dosage recommended for the treatment of gastroenteritis. In this country outbreaks of gastroenteritis are relatively common and it is often not possible to isolate a definite pathogenic organism. It is sometimes due to an organism of the Salmonella group but such cases are a minority. Sulphonamides have been used extensively in outbreaks of diarrhœa and vomiting, but as the condition is usually self-limiting the results are difficult to assess. In the absence of a bacteriological diagnosis it is more reasonable to use sulphonamides than the high-powered antibiotics. Several of the antibiotics may cause diarrhœa and vomiting as side-effects, apart from their cost, and they should not be used without a good reason.

If sulphonamides are used, phthalylsulphathiazole or succinylsulphathiazole are rational in view of their slow absorption rate. Phthalylsulpha-

thiazole, 3 g. daily, or succinylsulphathiazole, 10 g. daily, in divided dosage is the drug of choice. In children of five and upwards the dosage is roughly halved. Mixture of succinylsulphathiazole for infants B.P.C., which contains 0.5 g. in 4 ml., is a suitable preparation:—

Succinylsulphathiazole, in fine powder	7½ grains (0.5 g.)
Light kaolin	5 grains (0.3 g.)
Compound powder of tragacanth	½ grain (30 mg.)
Syrup of raspberry	15 minims (1 ml.)
Solution of benzoic acid	1¼ minims (0.08 ml.)
Solution of amaranth	½ minim (0.03 ml.)
Water	to 60 minims (4 ml.)

The relatively insoluble sulphonamides have also been used as preoperative and postoperative measures in surgery of the colon. If such treatment is prolonged it is usual to give vitamin B complex and vitamin K, as there is some evidence of diminished absorption of these substances. Sulphonamides have been used in the long-term treatment of ulcerative colitis, but without much success. When there is superadded infection sulphonamides will help and either succinylsulphathiazole or phthalylsulphathiazole may be tried.

IN SKIN DISEASES

Sulphonamide ointments are effective in treating various skin infections, but the risk of sensitivity reactions is so high that sulphonamides should not be used for this purpose now that other efficient treatment is available. A curious and unexplained phenomenon is the action of sulphapyridine in dermatitis herpetiformis. It is moderately consistent in producing improvement in the small dosage of 1 g. twice daily.

IN DISEASES OF THE EYE

The use of sulphonamides in ophthalmia neonatorum has already been referred to. Sulphonamides are also effective in a large proportion of cases of acute conjunctivitis and blepharitis. In adults, sulphacetamide drops ('albucid'), 30 per cent., are instilled six-hourly, preferably after a swab has been taken for culture.

PROPHYLACTIC USE OF SULPHONAMIDES

Sulphonamides have been used in cases of rheumatic fever in an attempt to reduce relapses and recurrences. The effectiveness of this prophylaxis is difficult to establish but many clinicians believe it to be worth while. Sulphamerazine is usually used and is convenient in that dosage can be infrequent in view of its slow excretion. The dosage is 0.25 g., or 0.5 g., twelve-hourly, according to the size of the child, and treatment is continued for three months after the acute infection and throughout the winter. Reference has already been made to the use of sulphonamides in preventing infection due to an indwelling catheter and in the surgery of the colon. Some practitioners give sulphonamides routinely to patients with measles in the

hope of preventing the complications of pneumonia and otitis media. The evidence is not conclusive.

ADMINISTRATION

Sulphonamides are usually administered by mouth and are absorbed at varying rates. The importance of this lies in the necessity of choosing the preparation to be used for a specific purpose. Mixtures may be used for children but they tolerate crushed tablets quite well.

Parenteral use is occasionally necessary when the patient is vomiting or unconscious as in meningococcal meningitis. The sodium salts of sulphathiazole, sulphadimidine and sulphadiazine are sufficiently soluble but highly alkaline. They may be administered intravenously or intramuscularly. If used intravenously as a 5 per cent. solution, the injection must be given very slowly and extravasation must be avoided as the solution is irritant and painful.

Sulphadimidine sodium and sulphathiazole sodium for intramuscular use contain 1 g. in 3 ml., whilst sulphadiazine sodium contains 1 g. in 4 ml. Here again great care must be taken to ensure that the injection is given deeply enough and well away from the sciatic nerve. The vastus lateralis should be used and consecutive injections must be at least three inches apart. Oral therapy should be substituted as soon as possible. Except in meningococcal infections parenteral sulphonamides have been largely replaced by the antibiotics. Sulphonamides should never be given intrathecally. A good concentration is obtained in the cerebrospinal fluid by oral, intravenous or intramuscular therapy, and intrathecal use is highly dangerous.

DOSAGE

The dosage of the various preparations has been indicated in each section. The underlying principle is to obtain an adequate blood level quickly and to maintain it. The loading dose is important and reduces the risk of the organism becoming sulphonamide resistant during the build-up period.

The total daily dose and the interval between doses vary according to the preparation used and it is particularly important to note the small dose of sulphamerazine and sulphamethizole.

The dosage for children, using sulphadimidine, is 0.3 g. per kg. body weight per day and the total should be divided into four-hourly doses. In meningococcal meningitis it is advisable to start with intramuscular sulphadimidine sodium. The dose by this route should be 0.1 g. per kg. per day, given four-hourly. Using sulphamethizole for urinary infections in children the dose should be 0.025 g. per kg. per day, divided into six-hourly doses.

TOXICITY

With the earlier sulphonamides many side-effects, including nausea and vomiting, headache, confusion, depression and cyanosis, were quite common,

but are seldom encountered with the preparations now available. They disappear rapidly on stopping treatment.

Fever due to sulphonamides is still quite common and is often associated with a sensitization rash. This usually occurs about seven to ten days after treatment has started and is varied in appearance. It may be erythematous, macular or vesicular. It commonly appears on areas of the body exposed to the light, and sunbathing and treatment with ultra-violet light should be avoided while taking sulphonamides. These rashes may occur following systemic or topical use of sulphonamides and were quite common when sulphonamide ointments were being used extensively. This form of local application should be abandoned. Skin sensitivity has considerable nuisance value in that the drug must be stopped and should not be given to that patient again.

The more serious effects of sulphonamides on the bone marrow are fortunately rare. Some degree of polymorphonuclear leucopenia is common and of little significance. Agranulocytosis occasionally occurs after seven to ten days, and it is probably due to sensitivity of the marrow in the particular individual, although it is more likely to occur with prolonged treatment. Sore throat, fever, and malaise should lead to a white cell count and treatment with antibiotics until the count has returned to a reasonable level. Hæmolytic anæmia, aplastic anæmia and thrombocytopenia have all been described following sulphonamide therapy, but are very rare.

The formation of crystals in the urine may occur during administration of most of the sulphonamides and may cause renal pain, hæmaturia, retention and, rarely, anuria. It can be prevented by ensuring an adequate fluid intake, especially in the presence of vomiting, diarrhœa or excessive sweating. Rendering the urine alkaline also decreases the risk and this should be done when giving sulphathiazole, sulphadiazine, sulphamerazine or sulphadimidine. By giving a mixture of sulphonamides the concentration of each in the urine is reduced. This reduces the risk of crystallization and is one advantage in using trisulphonamide, but little trouble should occur with single preparations given with the necessary precautions.

Toxic hepatitis, exfoliative dermatitis and polyarteritis nodosa have been ascribed to sulphonamides, but the evidence of cause and effect is not conclusive.

CONCLUSION

Sulphonamides are reliable, effective and inexpensive when used in adequate dosage against sensitive organisms. If good results are to be obtained, it is necessary to choose a suitable preparation for a specific purpose.

ANTI-TUBERCULOUS DRUGS

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It is just ten years ago, September 1946, that the Medical Research Council undertook to plan clinical trials of the antibiotic, streptomycin, discovered in 1944 by Waksman and his co-workers (Schatz, Bugie and Waksman, 1944) who carried out experiments on guinea-pigs infected with *M. tuberculosis*. Results of the action of the drug in clinical pulmonary tuberculosis were published by Hinshaw and Feldman (1945) a year later. By 1948 it was recognized that the combination of *para*-aminosalicylic acid (PAS) and streptomycin materially decreased the incidence of resistant strains of *M. tuberculosis*. Robitzek *et al.* (1952) reported favourably on the use of isonicotinic acid hydrazide (isoniazid) in advanced cases and the Medical Research Council immediately investigated this drug by clinical trials (1952), confirming its value and showing that when combined with streptomycin or with PAS the emergence of resistant strains was diminished. Further clinical trials (Medical Research Council, 1953, 1955) showed that daily streptomycin and isoniazid gave the best results, but that isoniazid with PAS was also satisfactory, as assessed after three and six months, which is of course a short period of observation. Evidence is now accumulating in favour of long-term chemotherapy: from six to eighteen months after the sputum has become negative, in all but minimal cases.

ACTION OF THE DRUGS

It is probable that streptomycin and PAS act on the *M. tuberculosis* in the tissue fluids and are bacteriostatic, preventing the growth of the bacilli, whereas isoniazid passes through the cell wall and gets into the macrophage cells containing the bacilli and may be bactericidal. It is obvious that lesions with a good blood supply, for example miliary and small exudative lesions, are brought into contact with the drugs, whereas caseous and chronic fibrotic or encapsulated disease may not allow suitable concentration of the drugs to affect the bacilli.

It is essential to send sputum for sensitivity tests before embarking on a second course of anti-tuberculous drugs, particularly when PAS alone has been given previously. Treatment can be started but may be modified later, according to the results of the bacterial sensitivity.

TOXIC EFFECTS

Streptomycin.—Dihydrostreptomycin may cause deafness and should not be used for long-term treatment. Streptomycin sulphate is most widely used and may cause vestibular damage, particularly in the elderly, but this is rare with a daily dose of 1 g. or until the total dosage has exceeded 150 to

200 g. Allergic reactions with fever, skin rashes and joint pains are observed in about 10 per cent. of cases, but on withdrawal of the drugs these symptoms disappear within forty-eight hours. Desensitization to the drug is relatively easy in most cases. Nurses and pharmacists handling the drug may get dermatitis of the hands or other parts touched by the drug and should wear rubber gloves when making up solutions and giving injections.

PAS.—Nausea, vomiting and diarrhœa are common symptoms, whereas hypothrombopenia, hepatitis and exfoliative dermatitis are very rare. Allergic reactions similar to those seen with streptomycin occur in at least 10 per cent. of cases: usually about the second or third week.

Isoniazid.—Toxic symptoms are unusual with the ordinary dose of 200 to 300 mg. daily (3 to 4 mg. per kg.). When the dose is increased above 8 mg. per kg., mental disturbances, nightmares, depression and epileptiform fits may be noted.

SCHEME OF TREATMENT

The extent and type of disease must be considered in planning treatment. Minimal exudative disease requires shorter and perhaps less intensive therapy than cavitated or fibro-caseous disease. Drugs should always be given in combination to diminish the emergence of resistant strains: it is usual for two drugs to be given together, with the idea of keeping the third drug in reserve should resistance develop. Some physicians give the three drugs together or in rotating pairs at various intervals of time.

The most efficient combination is streptomycin, 1 g. daily, with isoniazid, 3 to 6 mg. per kg. body weight (200 to 400 mg. daily for a patient weighing 10 stone [approximately 70 kg.]). This treatment is often given for twelve weeks, after which the streptomycin may be reduced to 1 g. thrice weekly for a further twelve weeks, giving a total dose of streptomycin of about 120 g. If clinical progress is satisfactory, with sputum conversion and cavity closure, many physicians change to daily PAS, 12 g., and isoniazid until it is decided to stop the drugs.

Streptomycin, 1 g. daily, with PAS, 12 to 20 g., is probably not such an effective combination and is more unpleasant to take. I only use this combination when there is evidence of resistance to isoniazid.

Isoniazid with PAS, 10 to 20 g. daily, has been shown by the Medical Research Council's trials (1955), with only six months' observation, to be a good combination although less effective than isoniazid with streptomycin. Oral as opposed to parenteral therapy has obvious advantages but I reserve this combination for the continuation course. In minimal disease, oral therapy may be sufficient but relapses are more common.

Various schemes of rotation of combination of the three drugs have been published but few have quoted sufficient cases observed for a reasonable time to be impressive. Recently the team at Guy's Hospital (Joiner *et al.*, 1956) has published the results of a two-year follow-up with detailed bacteriological, radiological and clinical observations on two groups of patients with

advanced pulmonary tuberculosis treated in the home. Treatment was continued for thirty-six weeks after the last positive bacteriological tests.

Group A cases were treated continuously with isoniazid, 250 mg., and PAS, 10 g., daily. Group B cases with the following rotation of drugs: weeks 1 to 4, streptomycin, 1 g. twice weekly, with isoniazid, 250 mg. daily; weeks 5 to 8, isoniazid, 250 mg., with PAS, 10 g., daily; weeks 9 to 12, PAS, 10 g. daily, with streptomycin, 1 g. twice weekly. The cycle was then repeated. At the end of two years, in Group A (14 patients) five were successful and nine failed. In Group B (13 patients) twelve were successful and one failed.

The deductions from this work are that in advanced chronic disease, the rotating treatment, including streptomycin, is highly satisfactory, whereas PAS and isoniazid are unsatisfactory. Treatment must be maintained for a long time: at least nine months after the sputum has become negative on smear and culture.

The cavity has long been considered the crux of treatment of pulmonary tuberculosis; collapse measures by medical or surgical means, or surgical resection have been the recognized treatment. With prolonged drug treatment cavities have closed and indications for surgical intervention have become less definite. Ross and Kay (1956) studied 138 patients with cavitated disease, of whom 92 were treated by chemotherapy alone, and 46 by additional collapse or resection. No relapses (positive sputum and radiographic regression) occurred in cases treated by chemotherapy for eight months or longer after apparent cavity closure as seen radiologically, whereas 11.6 per cent. per year relapsed when the duration of chemotherapy was less than four months.

A small proportion of cavities become cyst-like spaces and on resection many of these 'cysts' are lined with shining endothelium but on serial section minute areas of tuberculous granulation tissue may be seen, from which *M. tuberculosis* have been recovered. When chemotherapy has been continued for long periods, nine months to two years, these 'cysts' may in fact be sterilized and remain healed. An increasing number of these cases are now under observation after treatment has ceased, and it is yet too early to be sure that the disease is stamped out. The fact remains that the indications for surgical treatment of pulmonary tuberculosis have changed a good deal over the past three years.

DETAILS OF ADMINISTRATION

Streptomycin sulphate.—This is given intramuscularly, 1 g. dissolved in 3 ml. of water, and the nurse should be instructed as to the proper sites for injection. Riches (1954) reported that about 30 per cent. of patients develop unpleasant symptoms one to three hours after injection, when the level of the drug in the blood is maximum, particularly after exercise. Tingling in and around the mouth, giddiness, headaches and 'muzziness', with difficulty in accommodation, are the most frequent symptoms, which are ameliorated if not abolished when the injection is given in the evening. A convenient method, avoiding diluting or handling the drug, is the use of the Mitrex

medical cartridge syringe and 'viules' of streptomycin supplied by Boots Pure Drug Co. The dose should be recorded by the nurse every week on the temperature chart or in a diary kept by the patient, so that the physician can see at a glance the total dose received to date.

Para-*aminosalicylic acid* (*sodium salt*). *PAS.*—This may be taken in various ways, as a mixture, in cachets, in keratin-coated tablets or as a granulate, according to individual taste. A cachet containing PAS (sodium salt), 1.5 g., with isoniazid, 25 or 33 mg., is a convenient way of administering both drugs: e.g. 'pasinah 25' or 'pasinah 33' cachets (Wander Ltd.); two cachets four times daily gives a dose of 12 g. of PAS and 200 or 264 mg. of isoniazid.

DESENSITIZATION

Pyrexia is a common sign of an allergic reaction to either streptomycin or PAS, often appearing from ten to twenty-five days after starting the drug. With an unexplained fever this possibility should always be considered, and the diagnosis is confirmed when the temperature falls within a day or two of withdrawing the drugs. One has then to decide which drug is the cause: a single dose of PAS usually causes a pyrexia within a few hours and confirms that this drug is the culprit. If the test dose of PAS has no effect, an injection of 0.5 g. of streptomycin should be tried. Occasionally both drugs cause reactions at the same time.

Before starting desensitization it is wise to withdraw drugs for a week or ten days to allow the rash or other manifestation to clear. With PAS it is usually safe to start with 0.5 g. by mouth and if no reaction occurs to increase the dose each day as follows: 1, 2, 3, 4, 5, 7, 9 and 12 g. With streptomycin a common starting dose is 0.1 g. followed by 0.15, 0.2, 0.25, 0.3, 0.4, 0.5, 0.6, 0.8 and 1 g. An antihistamine such as chlorcyclizine ('histantin'), 50 mg. thrice daily, is an added safeguard.

Nurses and pharmacists with local skin sensitivity usually need much smaller doses or may be desensitized under a cover of corticotrophin.

CORTICOSTEROIDS

These have been used in combination with the anti-tuberculous drugs by various workers, with the idea of allowing better access of the drugs to the lesions in the lungs. Houghton (1956) has used corticotrophin in a carefully controlled series and has found rapid and sometimes dramatic clinical and radiological improvement in a high proportion of cases, without serious complications. This treatment is not yet in general use but has great potentialities.

OTHER DRUGS

Thiosemicarbazone, viomycin and tetracycline have all been used but their therapeutic efficacy does not approach that of the other three drugs.

Calcium 4-*benzamidosalicylate*, '*therapas*' (Smith and Nephew Ltd.), was investigated by Bavin and James (1953). It is broken down in the body, liberating 47.6 per cent. of *para*-aminosalicylic acid and benzoic acid. Given

in a dose of 3.5 g. as a powder in milk four times daily, it rarely causes intestinal upset and is not so unpleasant to take as PAS.

Gibson and Nagley (1955) treated 204 unselected cases with the drug in combination with either streptomycin or isoniazid. Only 121 patients had positive bacteriological cultures immediately before starting the drug and the majority had received antibacterial drugs previously. The authors considered that 'therapas', in dosage of 14 g. daily, was equivalent to PAS in similar dose but admit that the period of follow-up was too short to be of scientific value.

Further observations are required before accepting that the drug equals PAS in efficacy.

Isonicotinic acid hydrazide-p-*aminosalicylate*, '*dipasic*' (Bengue and Co. Ltd.), contains 47 per cent. of isoniazid and 53 per cent. of PAS in chemical combination. The recommended dose is 100 mg. per 20 lb. (9 kg.) body weight. It is supplied in tablets of 100 mg. and the usual dose is 700 to 1000 mg. daily.

Clegg (1955) treated seventeen patients with advanced cavitated disease—who had previously been treated by antibacterial drugs for periods of six years to three months—with 'dipasic', 600 mg. daily for three months. At the end of this period six cases had negative cultures; in ten cases the quantity and bacterial content of the sputum were much reduced and only one patient showed no alteration in the sputum. Further trials are impending.

At the present time I know of no scientific evidence that the drug is as efficient as isoniazid and PAS.

SUMMARY

Although new drugs are on trial it is wise to continue with those of proved worth. Isoniazid with daily streptomycin is the best combination and is often given for three to four months, followed by streptomycin thrice weekly with daily isoniazid until sputum or laryngeal swab smears and cultures have been negative for six months. Daily isoniazid with PAS, 12 g. daily, is a good continuation course, the duration of which depends upon the individual case, but there is much to be said for continuing for a minimum period of nine months after sputum conversion.

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THE BARBITURATES AND OTHER SEDATIVES

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Chemical enterprise in modern times has been most fertile in the field of synthesis of sedative and hypnotic agents. Many hundreds of these drugs have been studied pharmacologically and scores have been introduced into medical practice under a bewildering variety of names—a tribute to the inventive ingenuity of the pharmaceutical manufacturers. As it has been put upon the market each new drug has been claimed to be free from undesirable side-effects, to be non-habit-forming, and to have a wide margin of safety between hypnosis and medullary depression, but it is safe to say that there is no paragon which possesses all these desirable attributes.

USE OR ABUSE?

Surveys of the prescriptions issued under the National Health Service in Scotland and in Great Britain in 1949 and 1951 respectively showed that prescriptions for hypnotics and sedatives formed some 15 per cent. of all drugs prescribed. In 1952, the United States pharmaceutical industry produced and sold 300 tons of barbiturates, representing well over one billion doses of this particular type of hypnotic alone. It is a significant commentary on the tensions and pressures of present-day conditions, or on the prescribing habits of doctors, that such drugs should constitute far the largest single group of prescriptions, and there is every reason to suppose that the proportion has increased in the last few years.

It is perhaps slightly paradoxical to find that the use of amphetamine has also vastly increased. No doubt this is to some extent the result of its frequent employment in the treatment of obesity, but it is also widely prescribed for its stimulant effect on the central nervous system. This simultaneous increase in the number of prescriptions for depressants and stimulants of the central nervous system can be ascribed in part to our 'stop and go' method of modern living which like our 'stop and go' motor car driving is apt to be very wearing on the mechanism. The average city dweller seems to want to turn consciousness off and on like a tap. 'I don't know', says the young woman in the *New Yorker*, 'whether to take a benzedrine and go to the party or to take a seconal and go to bed'.

SOME GENERAL PRINCIPLES

We are profoundly ignorant of the function of sleep and of the number of hours of sleep required either to maintain health or to recover from bodily or mental illness. Nevertheless, no-one who is in daily contact with sick

people can fail to have been impressed by the therapeutic value of a 'good night's sleep' for those suffering from cardiac failure, acute infections or anxiety states; and few will contest the propriety of giving a hypnotic, for a few nights at least, in such conditions. What is much more controversial is the practice of 'sedating' during waking, and often working, hours, people whose symptoms are the result of worry and frustration, and those suffering from what it is now fashionable to call psychosomatic disorders. Of the barbiturate group of drugs, those whose duration of action is limited to four or eight hours are appropriately used for inducing sleep, whilst sedation calls for the use of longer-acting drugs like phenobarbitone. Nevertheless, the prescriptions issued in Britain for phenobarbitone are between two and three times more numerous than those for the short-acting barbiturates so that it would appear that the bulk of any excessive prescribing of barbiturates is accounted for by phenobarbitone.

Neuroses constitute the biggest problem facing the general practitioner, and until the demands on his time can be reduced, faced with the alternatives of discussing his patients' troubles—a lengthy process—and writing a prescription, he will too often, of necessity, choose the shorter and easier course, even though he knows perfectly well that the prescription of a mixture or a tablet will not heal a broken heart or liquidate his responsibilities as a wise and sympathetic counsellor. As a placebo, it seems that the prescription of a sedative has now largely taken the place of the bitter tonic so beloved of our forefathers, which latter had at any rate few harmful effects. The sedative, on the other hand, has a potent depressant action, which may be undesirable, and carries with it the danger of dependence and even addiction. Placebos should seldom be given in the treatment of purely neurotic disorders since the patient will think, quite logically, that the giving of medicine indicates at least some element of organic illness. Sedatives should be used sparingly in the treatment of neurosis and only for patients with severe anxiety states.

It is a platitude that no drug is a substitute for a full history, full examination, reassurance and explanation. It is also important before resorting to hypnotics to attempt, when possible, to remove the various prosaic exogenous and endogenous stimuli which militate against sleep in any particular case: cold feet, an unduly chilly or stuffy bedroom; an overfilled or a very empty stomach; an overloaded bowel or an overdistended bladder; pruritus, pain and bodily discomfort of all kinds; and particularly emotions of anger, fear, guilt, worry or love.

CHLORAL HYDRATE

Chloral hydrate, synthesized in 1832 and introduced into medical practice in 1869, was the first of the synthetic hypnotics and immediately attained great popularity. Previously the bromides and drugs made from 'poppies or mandragora' were the only 'drowsy syrups' available and chloral was regarded initially as an innocuous remedy without the drawbacks of the opiates. In consequence it was often used in a carefree, indiscriminate

manner. The not infrequent fatalities which resulted endowed it with an unenviable notoriety as being toxic to the cardiovascular system. There is no reason to suppose that in therapeutic doses chloral is more culpable in this respect than equivalent doses of modern hypnotics. Indeed, its process of inactivation in the body prevents chloral from readily producing a cumulative action.

Chloral exists in the form of white crystals which have a disagreeable taste and are completely soluble in water. They are too hygroscopic to be prescribed as tablets or in ordinary capsules, and chloral is one of the few drugs for oral use which must always be prescribed in solution. If the crystals are applied to the skin surface they have a rubefacient action and eventually may even cause vesication. Chloral is thus irritating to the empty stomach and should be prescribed as a well-diluted draught with a strong flavouring agent to conceal its taste. The usual dose is 1 to 2 g. (15 to 30 grains).

It usually produces within half an hour sleep which is quiet and deep though not as a rule dreamless and which lasts for from six to eight hours according to the dose. There is little 'hangover'. When pain accompanies insomnia, 1 ml. (15 minims) of the tincture of opium can be conveniently prescribed with the chloral, which makes an admirable hypnotic-analgesic mixture:—

Chloral hydrate	1.3 g. (20 grains)
Tincture of opium	1 ml. (15 minims)
Syrup of orange	2 ml. (30 minims)
Water.....	to 15 ml. (½ fluid ounce)

1 tablespoonful at bedtime, diluted with a wineglass of water.

Chloral seems to be the most suitable sedative for irritable infants, who respond well to 60 mg. (1 grain) given before each feed:—

Syrup of chloral	0.4 ml. (7 minims)
Liquid extract of liquorice	0.2 ml. (3 minims)
Glycerin	0.6 ml. (10 minims)
Water.....	to 4 ml. (60 minims)

There are no therapeutic roses without their thorns and the disadvantages of this excellent and inexpensive hypnotic which has stood the test of time are its disagreeable taste, its nauseating tendency and the fact that it cannot be given in the convenient form of tablets or capsules. These disadvantages may be advantages from another point of view. Thus the tendency to continue its use in a careless manner is minimized in the case of a medicine which has to be prescribed in a solution and which has a disagreeable taste, in comparison with a drug which can be conveniently carried and swallowed in tablet form. In consequence habituation, addiction and acute poisoning are rarely seen nowadays as the result of chloral.

BROMIDES

Bromides are often prescribed in conjunction with chloral or even alone as hypnotics. This is irrational if the mixture is to be used as a single-dose

hypnotic. The therapeutic action of the bromides depends upon the replacement in the brain of chloride with bromide ions—a process which is only slowly effected, so that a single dose of bromide will have no more hypnotic effect than a dose of salt water. It takes some days for a daily dose of 3 g. (45 grains) to produce a blood concentration of 80 to 100 mg. per 100 ml.—the level at which powerful therapeutic sedation is commonly attained—but the depression produced is insufficiently selective to induce sleep without causing undesirable drowsiness throughout the twenty-four hours. The cumulative effect of prolonged bromide administration is inadequately appreciated, for chronic poisoning is not uncommon. When the concentration in the blood reaches 100 mg. per 100 ml., about 15 per cent. of the chlorides have been replaced by bromides and when the concentration rises much above this figure signs of bromism result. These are stupidity, depression, muscular weakness, incoordination and pustular skin rashes. The nervous symptoms of bromism may be mistaken for exacerbation of the disease for which the bromide was originally prescribed and in consequence the dose may be increased still further. Bromide psychosis is thus not uncommon in patients admitted to mental hospitals.

As occasional hypnotics bromides are worthless, and as sedatives and anticonvulsants there is nothing they can do that other drugs cannot do better with fewer side-effects. In my opinion they should be regarded as being in that group of drugs, at one time valuable, which, with the advent of more effective and less toxic alternatives, should now be relegated to the therapeutic lumber-room.

PARALDEHYDE

Paraldehyde is a colourless volatile liquid. It decomposes in sunlight and should be stored in an amber-coloured container. It has a characteristic odour and an unpleasant burning taste. Because of its poor solubility and disagreeable taste it is difficult to dispense.

It is readily absorbed when given orally, rectally or intramuscularly. When given intramuscularly care should be taken to avoid nerve trunks since it may cause nerve injury resulting in paralysis. When given as a retention enema it should be dissolved in two parts of olive oil which helps to diminish any rectal irritation which paraldehyde may induce. The usual oral and intramuscular dose is 2 to 8 ml.; larger doses can be given in serious delirious states. When used as a basal anæsthetic in the form of a retention enema, 15 to 30 ml. are used depending upon the weight of the patient.

The action of paraldehyde on the central nervous system is fundamentally similar to that of alcohol, but its hypnotic effect is more powerful and usually sets in within fifteen minutes of oral administration. The sleep produced is normal and there are few after-effects. Indeed, paraldehyde has a larger margin of safety than any other sleep-producing drug and large quantities can be taken without a fatal result. Nevertheless, it is disagreeable to take and imparts an unpleasant persistent odour to the breath. Thus, it should seldom be given orally or as a hypnotic for ordinary individuals.

Its chief use is by intramuscular injection for the control of unmanageable delirious patients—particularly in delirium tremens and in status epilepticus; and per rectum as a basal anæsthetic. For these purposes it is a valuable drug.

THE BARBITURATES

The barbiturates have a wide range of action and, being in tablet form, are conveniently carried and readily administered. The fate of a particular barbiturate in the body depends upon its chemical structure. The relative speed with which it is destroyed, absorbed by the tissues and eliminated by

	Official preparation *British Pharmacopœia*	Proprietary name	Dose	Approximate duration in hours
LONG ACTING	Phenobarbitone	Gardenal; Luminal	30 to 120 mg.	12 to 24
	Phenobarbitone sodium	Gardenal sodium; Luminal sodium	60 to 200 mg. intramuscularly	12 to 24
	Barbitone	Veronal	250 to 500 mg.	10 to 20
	Barbitone sodium	Medinal; Veronal sodium	250 to 500 mg.	8 to 16
INTERMEDIATE ACTING	Allobarbitone	Dial	100 to 200 mg.	8 to 10
	Butobarbitone	Soneryl	100 to 200 mg.	8 to 10
	Amylobarbitone	Amytal	100 to 200 mg.	6 to 8
	Pentobarbitone	Nembutal	100 to 200 mg.	6 to 8
SHORT ACTING	Cyclobarbitone	Phanodorm	100 to 200 mg.	4 to 6
	Quinalbarbitone	Seconal	100 to 200 mg.	4 to 6
	Hexobarbitone	Cyclonal; Evipan	250 to 500 mg.	3 to 4

TABLE I.—Dosage and duration of action of the barbiturates.

the kidneys will determine its duration of action. Thus, depending upon the barbiturate employed, the dose and method of administration, continuous mild sedation, an eight hours' sleep or a short general anæsthesia may be produced. Unless they impair consciousness, barbiturates, like the hypnotics already discussed, have little analgesic effect and cannot be relied upon to produce sleep in the presence of pain. Combined with aspirin they may prove effective when the pain is of moderate intensity.

For hypnotic and sedative purposes barbiturates may be classified as long-acting, intermediate-acting, or short-acting. Usually the interval between the administration of the drug and the onset of therapeutic effect also corresponds to this classification. Table I shows approximately their duration of action which, however, varies with the dose employed. In addition, patients show considerable individual variation in this respect.

Phenobarbitone should never be used as a hypnotic. It is a long-acting sedative for use in anxiety states and in such disorders as hyperthyroidism, asthma and peptic ulcer, in which sedation may be a desirable part of treat-

ment. In addition it has a specific depressant action on the motor cortex and is the sheet anchor of treatment in grand mal epilepsy: 0.2 g. (3 grains) of its sodium salt may be injected intramuscularly or very slowly intravenously in status epilepticus. Phenobarbitone is rarely effective in petit mal, and is contraindicated in paralysis agitans as it may aggravate the rigidity.

There seems little need nowadays for the use of the original ***barbitone*** or of its sodium salt. For most patients the choice of an appropriate hypnotic may be made from the barbiturates of medium or short duration. As a profession we are often injudicious in this choice. When such a wide range of agents is available it gives scope for some artistry in choosing the appropriate drug for the particular occasion. For example, when a business man requires a hypnotic for a night journey it is unwise to prescribe barbitone which will not put him to sleep for an hour or more, or permit him to surface from its ultimate effect till towards the end of his meeting the next morning.

When a patient has difficulty in falling asleep the short-acting drugs such as ***quinalbarbitone*** or ***cyclobarbitone*** are suitable. There is no significant difference in their efficacy or action, but quinalbarbitone, being a little cheaper, is probably the drug of choice. Tablets of ***hexobarbitone*** have too evanescent an effect to make them reliable hypnotics for most people. When patients complain that they waken during the early hours of the morning —the common form of insomnia of old people—the medium-acting barbiturates are more suitable. Of these, ***butobarbitone*** is the cheapest.

The most usual manifestations of idiosyncrasy to barbiturates are skin rashes resembling the diffuse rashes of the exanthemata. The danger of acute barbiturate poisoning is common knowledge, and such poisoning ranks only second to gas poisoning as the cause of suicidal deaths. The fatal dose is seldom less than twelve times the therapeutic dose, although a fatal issue may result from a smaller dose taken with alcohol which greatly potentiates the effect of barbiturates. The new barbiturate antagonists—bemegride ('megimide') and amiphenazole ('daptazole')—have supplanted analeptics in the treatment of such acute poisonings. Chronic intoxication with barbiturates is also on the increase. It is no longer possible to deny the existence of a state of dependence on these drugs which fulfils all the criteria for addiction.

CARBROMAL

Carbromal is a monoureide and is readily eliminated, being largely decomposed in the body to urea and to an inorganic bromide. It was originally introduced with the idea that it would combine the sedative effects of bromide with the narcotic action of the aliphatic series, but the bromide component cannot play an important part in the action. Given in doses of 0.6 to 1.2 g. it is a mild and innocuous hypnotic.

'Sedormid' (allyl*iso*propylacetylurea), another urea derivative, which contains bromine and has been extensively used as a hypnotic, should not be employed owing to its liability to produce agranulocytosis and thrombocytopenic purpura.

METHYLPENTYNOL

The much-advertised new preparation, methylpentynol ('oblivon'), is neither a barbiturate nor a ureide but a simple unsaturated aliphatic carbinol. It is a colourless liquid with a pleasant odour but a somewhat burning and persistent taste, so that it is usually dispensed in soft gelatin capsules, each containing 250 mg. of the drug. The hypnotic dose varies from 1 to 3 capsules. Methylpentynol is rapidly metabolized and excreted in the urine so that it has a very evanescent action of not more than three or four hours. It may cause annoying eructations. Serious side-effects are rare but include exfoliative dermatitis and hepatitis. It would not appear to be superior to, or even as effective as, the short-acting barbiturates.

TRANQUILLIZERS

Numerous new compounds have been produced recently which have a more selective depressant action on the brain than those already mentioned. It is now fashionable to call these drugs 'tranquillizers' rather than 'sedatives'. Their exact mode of action is unknown, but it is tempting to speculate that their effects are mediated by liberating 5-hydroxytryptamine or by antagonizing lysergic acid diethylamide. Chlorpromazine ('largactil') and reserpine are the tranquillizers which have had the most prolonged and extensive clinical trial and have been widely used to allay restlessness and anxiety.

Apart from its remarkable action in certain psychotic conditions, chlorpromazine enhances the effect of analgesics and sedatives and often abolishes nausea and vomiting. Possibly therefore its most important role is in the management of the terminal phases of hopeless conditions such as inoperable cancer. Its side-effects include serious jaundice, agranulocytosis and hypotension, especially in elderly patients. Reserpine is notoriously prone to cause severe depression with suicidal tendencies. In addition, these drugs seriously interfere with the efficiency of workers, lowering their attention and making them absentminded, unobservant and lacking in initiative. They are also expensive. Thus, should a sedative prove necessary in the treatment of the more minor anxiety states commonly encountered in practice it is wiser, in the present state of our knowledge, to employ phenobarbitone.

SUMMARY

My favourite hypnotic and sedative preparations are as follows:—

For irritable infants—syrup of chloral.

When a hypnotic-analgesic is required—chloral hydrate and tincture of opium.

For delirium and status epilepticus—intramuscular paraldehyde.

When a long-acting sedative is required and for grand mal epilepsy—phenobarbitone.

When a short-acting hypnotic is needed—quinalbarbitone ('seconal').

For the early morning wakefulness of old age—butobarbitone ('soneryl').

ANALGESICS

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In a world where barbiturates are by every bedside and tranquillizers can be obtained from slot machines, it is not surprising that fortitude is at a discount and the public insistent on speedy relief of pain. The purpose of this article is to assess the plethora of analgesic drugs, endeavouring to steer a course between the Scylla of over-caution and the Charybdis of indiscriminate prescribing from the latest litter of the breakfast table.

SOME COMMONPLACE OBSERVATIONS

(1) That individuals vary greatly in their sensitivity to pain and it is by the art, as much as by the science, of medicine that suffering is assessed and the right dose of drug prescribed. (We must count ourselves lucky that so far there is no pain-meter or other instrument of precision to confuse the issue.)

(2) That it takes at least a year fully to understand the vagaries of a new drug and therefore, since life is short, it is wise to use few preparations and to know them well. It was said of that great clinician, Boerhaave, that as his experience widened, he reduced his list of drugs so much that ultimately he confined himself to bicarbonate of soda.

(3) That, whilst the *National Formulary* provides an excellent reference (16 analgesics and antipyretics, and 8 pure analgesics in the 1955 edition), yet advances often come from commercial firms and their latest additions should not necessarily be ignored on principle. Scrutiny of the prescriptions of many consultant physicians suggests that they have not forgotten this maxim.

(4) That tablets, capsules or injections are convenient and efficient methods of administering drugs and are nowadays generally preferred, except in the case of children, to the traditional bottle of medicine.

SALICYLATES AND OTHER MILD AND FREQUENTLY USED ANALGESICS

Acetylsalicylic acid.—Whatever else one may think of the Germans, tribute must be paid to their 19th century chemists who produced the mighty aspirin. Acetylsalicylic acid tablets, 5 grains (0.3 g.), or better, acetylsalicylic acid soluble tablets, should be the sheet anchor for minor aches and pains and, considering the millions that are swallowed each year, it is as safe a drug as one could wish for. Not only for trivial ailments, but in rheumatoid arthritis and rheumatic fever, aspirin has proved its value. In the former the Medical Research Council investigations showed that its effect was

as good as cortisone in early cases of the disease. In the latter it is probably better than sodium salicylate, because, as Micks points out, the sodium intake with large doses might adversely affect a failing heart. The maximum dose required for either condition is usually 10 grains (0.6 g.) of soluble aspirin two-hourly. In infancy aspirin can be given as acetylsalicylic acid mixture for infants N.F. (2 grains [0.12 g.] of aspirin in 60 minims [4 ml.] and pleasantly flavoured.) It should, however, be remembered that aspirin mixtures deteriorate rapidly and, except in infants, the tablet form is preferred. The use of aspirin gargled and swallowed, particularly after tonsillectomy, should also not be forgotten.

Mixtures of analgesics are said not to be more effective than a single drug, but acetylsalicylic acid compound tablets B.P.C. (A.P.C. tablets), are traditional and give excellent relief from minor pain while still enabling a patient to be at work.

Aspirin occasionally causes gastric erosion with hæmatemesis, and dyspeptics should always use the soluble form ('gone in 20 seconds') or *chew* the usual tablet. In 99 cases out of 100 the aspirin-doesn't-suit-me patient means the drug is too plebeian; where this is so it may be excusable to give a proprietary preparation with a different name, and convenient for this is 'ekammon'. The 100th case, usually that most enigmatic of problems, the asthmatic female, may on taking aspirin develop alarming symptoms—bronchospasm and peripheral circulatory failure—demanding urgent treatment. When such sensitivity is suspected, non-aspirin analgesics are available: phenacetin tablets B.P., 5 grains (0.3 g.), phenacetin and caffeine tablets B.P.C., or the proprietary drugs, 'saridone' or 'panadol' (both very expensive). 'Panadol' (the active metabolite of phenacetin)—'no aspirin, no phenacetin, no codeine'—has received a good deal of publicity recently, but an experienced family doctor reports that except for aspirin-sensitive patients it has no advantages over soluble aspirin.

Curious nomenclature and prescribing anomalies exist with aspirin. Thus, of the soluble preparations, 'solprin' and 'disprin' are identical and produced by the same firm. 'Solprin', because it is tax free, cannot readily be bought without a prescription, and 'disprin', as it is advertised to the public, cannot be prescribed on E.C. 10. The important point is that 'solprin' costs the National Health Service considerably more than soluble aspirin N.F. On the other hand, there is little difference between the over-the-counter price of soluble aspirin tablets and 'disprin', and the silver paper wrappings of the latter are useful in preventing deliquescence.

Codeine.—'Of little value in relieving pain' (Douthwaite). 'Has a negligible narcotic and analgesic action' (Micks). The codeine muddle is largely iatrogenic. Codeine compound tablets should never have been so named because their action depends upon aspirin and phenacetin (4 grains [0.25 g.] of each) and not on the codeine content ($\frac{1}{8}$ grain [8 mg.] only). In analgesic action therefore two compound codeine tablets nearly equal four of aspirin and that is why they work so well. For toothache, neuralgia, migraine,

sinusitis and for the aches and pains of febrile conditions such as influenza they are unrivalled. 'Veganin', almost identical, preceded the *National Formulary* prescription and deserves special mention. Unfortunately, the Formulary Committee does not allow for the costiveness of codeine, and it is left to a commercial firm to produce 'hypon' (essentially codeine compound tablets + phenolphthalein), a good but expensive combination, to overcome this disadvantage. There seems no doubt that well-regulated bowels *are* 'made stupid' by a dose as small as ¼ grain (16 mg.) of codeine phosphate. Codeine is also of value as codeine phosphate, ½ grain (30 mg.) for painful bowel spasms such as occur in irritable colon and intestinal hurry.

Patients with rheumatoid arthritis not infrequently prefer codeine + aspirin to aspirin alone and when they do there seems to be a good case for 'codis' (inexpensive) over codeine compound tablet. In 'codis' the aspirin is soluble and when large doses are being taken (8 to 10 tablets a day) there is less likelihood of gastric irritation.

There remain two other attractive types of analgesic combinations for which full credit must go to commercial firms. The first of these is analgesics combined with hypnotics: e.g. 'sonalgin' (butobarbitone, 1 grain [60 mg.], phenacetin, 3½ grains [0.21 g.], codeine phosphate, ⅛ grain [10 mg.]), which is useful at night in conditions such as rheumatoid arthritis; 'tercin', which is primarily analgesic (aspirin, 5 grains [0.3 g.], phenacetin, 3 grains [0.2 g.]), but also containing butobarbitone (½ grain [30 mg.]) to allay apprehension. The other is analgesics combined with central stimulants: e.g. 'edrisal' (aspirin, 2½ grains [0.15 g.], phenacetin, 2½ grains [0.15 g.], amphetamine, 2.5 mg.)—a remarkably efficient preparation in the treatment of dysmenorrhœa.

A final word of warning. Prescribe all the above 'for occasional use only'. Do not allow patients to regard the tablets simply as 'their' aspirin: addiction to barbiturates and to amphetamine *is* a very real danger.

Dover's powder.—Thomas Dover (1660-1742), ship's surgeon, buccaneer and rescuer of Alexander Selkirk, dosed his pirates to good effect with opium and ipecacuanha powder. Today the *National Formulary* lists three strengths—1 grain (60 mg.), 5 grains (0.3 g.), and 10 grains (0.6 g.)—of ipecacuanha and opium tablets, and also acetylsalicylic acid with ipecacuanha and opium tablets, a very suitable preparation for children: each tablet contains 2½ grains (0.15 g.) of aspirin and 2½ grains (0.15 g.) of Dover's powder. Although they contain opium, the tablets can be obtained without prescription (on 'signing the book'), the emetic properties of ipecacuanha countering addiction. Dover's powder ensures a good night's rest in feverish illnesses associated with painful cough and its unrivalled properties deserve more frequent prescription.

ANALGESICS OF MEDIUM POTENCY

Here are grouped together analgesics not far removed in potency from morphine but with less narcotic action.

Pethidine (demerol in the United States) holds pride of place and is invaluable. Respiratory depression is minimal, nausea and vomiting are less common than with morphine and the only drawbacks are dizziness, sweating and occasional cardiac arrhythmias. It can be given either in tablet form (50 mg.)—25 mg. is useless for adults—or by injection (50 to 100 mg.). A practitioner reports that in severe brachial neuritis he only obtained relief with intramuscular injection. His nightly ritual was butobarbitone tablets B.P.C., 3 grains (0.2 g.), followed one hour later by pethidine, 100 mg. intramuscularly. Rapid oblivion ensued and not a moment's sleeping time was wasted. Prolapsed discs, pleurisies, fractures and any conditions where pain is less than agonizing are indications for its short-term use. Addiction, however, is not uncommon and should be strongly guarded against unless incurable disease is present.

Levorphanol ('dromoran'), a synthetic derivative of morphine, is an effective analgesic, again with little narcotic action, but resembling morphine in that it depresses respiration and causes nausea and vomiting. It is said, however, to produce less mental depression than morphine after the analgesic effect has passed off. The dose is one or two 2-mg. tablets orally, or 2 to 4 mg. by injection. It seems to have no advantage over pethidine (except that its hypnotic action may be slightly less), and a pharmacist reports that he dispenses little—'and all to one patient with a painful amputation stump'. A general practitioner confirms the drug's efficacy but also the marked danger of addiction. Personal experience has shown it to be of use in keeping very comfortable over three years a patient with metastasizing carcinoma of the prostate held in check by stilbœstrol.

Methadone, usually called by its trade name 'physeptone', has morphine-like properties and is widely used in the form of its linctus, the dose of which is 60 minims (4 ml.). It is most efficient for irritating and painful coughs but the indications should be definite and it should not be prescribed indiscriminately. Often equally effective (and cheaper) are: squill opiate linctus B.P.C., which contains 20 minims (1.3 ml.) of camphorated tincture of opium B.P.; codeine linctus B.P.C.; codeine linctus, strong, N.F.; benzocaine compound lozenges B.P.C.; or even liquorice lozenges B.P.C., the well-known Brompton cough lozenge. Methadone is also useful as a general analgesic either in tablet form (methadone hydrochloride tablets B.P., 5 mg.) or by subcutaneous or intramuscular injection (5 to 10 mg.). The effective dose is about the same as that of morphine, although the drug is much less hypnotic.

Its main use is as a daytime medium analgesic for a bed patient who wishes to have his pain relieved without falling asleep. It should not be given to ambulant patients because it often produces marked dizziness and vomiting. Because of its depressant effect on the fœtus, it is contraindicated in obstetric practice. Addiction may be less troublesome than with morphine but should be remembered. Phenadoxone ('heptalgin'), a derivative of methadone, is not recommended. It has no advantages over methadone and

causes more dizziness. One general practitioner reported: 'It knocked one of my patients right out'.

Two older analgesic preparations in this middle range of potency must now be mentioned. The famous 'Mist. $\frac{2}{15}$'—combined sleeping draught and pain reliever—is particularly valuable in cardiac cases:—

Chloral hydrate	15 grains (1 g.)
Tincture of opium (or 'nepenthe')	15 minims (1 ml.)
Chloroform water	to $\frac{1}{2}$ fluid ounce (15 ml.)

It should be noted that 15 minims (1 ml.) of tincture of opium = $\frac{1}{6}$ grain (10 mg.) of morphine. The mixture should therefore *not* be prescribed 't.d.s., p.c.'.

Solution of morphine hydrochloride B.P. (5 to 30 minims [0.3 to 2 ml.]) is the treatment of choice for intractable pain such as may occur with carcinoma of the stomach and occasionally with large gastric ulcers. It is of great value because it can be added to, or taken away from, a mixture without the patient's knowledge.

POWERFUL ANALGESICS

'Man made aspirin; morphine came from heaven'. *Morphine* by injection, with its potent analgesic and narcotic effect, remains the classical treatment for conditions such as coronary thrombosis, biliary and renal colic, and in surgery for perforations and the pain and shock from injuries. The usual dose of $\frac{1}{4}$ to $\frac{1}{3}$ grain (16 to 20 mg.) is well known, but occasionally, in very big patients, $\frac{1}{2}$ grain (30 mg.) may be needed. If the pain is agonizing, or in severe shock, $\frac{1}{6}$ to $\frac{1}{4}$ grain (10 to 16 mg.) may be given intravenously, but indications must be stringent.

It should be remembered that probably more patients have died from too much morphine than from too little and in an emergency there is particular danger of successive doses being given. In patients sent to hospital it is therefore most important that the doctor should state clearly when and how much morphine has been administered. In accident cases a label should be attached to the patient. If an 'acute abdomen' is suspected, morphine should be withheld until treatment is decided upon. Infants may be alarmingly sensitive to morphine and small doses only should be given (see page 42). In the very old, too, it should be used with caution. An old lady of 92, given $\frac{1}{4}$ grain (16 mg.) of morphine for a fractured femur, went into coma from which she never recovered. When in doubt it is better by far to give a small dose, e.g. $\frac{1}{8}$ grain (8 mg.), and to repeat if necessary in half an hour. Morphine is tolerated badly in myxœdema, may precipitate coma in liver disease, is dangerous in emphysema and lethal in status asthmaticus. Vomiting often follows morphine and there is no way of preventing it. It is far more troublesome, however, if the patient is ambulant, and occurs infrequently when pain and shock are severe. The corollary to this is to use less potent preparations when suffering is difficult to assess.

Some favour *papaveretum* ('omnopon') and claim that nausea is reduced,

but dose for dose with morphine this is doubtful. Papaveretum injection B.P.C. contains in 1 ml. the equivalent of $\frac{1}{6}$ grain (10 mg.) of morphine, whilst the $\frac{1}{6}$-grain (10 mg.) tablet contains $\frac{1}{12}$ grain (5 mg.) of morphine. Dihydromorphinone ('dilaudid') is useful for patients who cannot tolerate morphine. The dose is about one-fifth that of morphine. The oral tablets contain $\frac{1}{25}$ grain (2.5 mg.), and hypodermic tablets $\frac{1}{32}$ to $\frac{1}{16}$ grain (2 to 4 mg.).

It is often stated that the sublingual dosage of morphine preparations is twice the hypodermic, but for bad pain it is by no means as effective. Still less are morphine suppositories: 'dispense with them' is a pharmacist colleague's view after personal experience.

The smoke of battle still lingers over *heroin*, and for a practising physician there is the dilemma that those who clamour for retention of the drug often decry it in their books. If given, its main place should be for bringing analgesia and peace of mind to those who have not long to live, and for this it seems superior to morphine: six-hourly injections of $\frac{1}{8}$ grain (8 mg.) produce the desired effect.

Chlorpromazine ('largactil') may prove (with morphine) a rival. It has excellent anti-emetic properties, frees the mind from worry and potentiates the sedative action of morphine. In combination therefore the two are very effective in controlling intractable pain when vomiting is also present: jaundice is a risk, but matters little in such circumstances. The initial dose by mouth is 25 mg. eight-hourly; the effective dose for general medical purposes lies between 75 and 150 mg. a day. By intramuscular injection, which is painful, the dose is 25 to 50 mg. thrice daily. It must *not* be injected subcutaneously.

Then there is amiphenazole ('daptazole') for concurrent use with large doses of morphine, and given to counteract respiratory depression. The first day of administration is usually a nightmare of needles. Subsequently one tablet (20 mg.) of amiphenazole is given with each morphine injection: usually between $\frac{3}{4}$ grain and $1\frac{1}{3}$ grains (45 and 80 mg.) eight-hourly. For pain in carcinoma when emphysema is a problem the drug is worth considering, but let not dying painlessly become too complicated. For many the needle is unnecessary, and all that is required is 'mist. euphoriens', that famous Brompton requiem:—

Morphine hydrochloride	$\frac{1}{6}$ to $\frac{1}{4}$ grain (10 to 16 mg.)
Cocaine hydrochloride	$\frac{1}{6}$ grain (10 mg.)
Clarified honey	60 minims (4 ml.)
Brandy	120 minims (8 ml.)
Water	to 1 fluid ounce (30 ml.)

To be taken as often as required.

The original formula was improved by giving gin (not brandy) but E.C. 10's prescribing gin are liable to be charged to the doctor. A way of getting round this is to prescribe the 'gin' as follows:—

Rectified spirit 120 minims (4 ml.) with tincture of capsicum $\frac{1}{2}$ minim (0.03 ml.)

Alternatively and cheaper, (to the community), is to prescribe no alcohol

and for the patient to take the mixture in the medium he fancies.

FAVOURITE ANALGESICS FOR SPECIFIC COMPLAINTS

CARDIOVASCULAR SYSTEM

Angina pectoris.—Lord Horder told us in 1950 (*The Practitioner*, 1950, **165**, 9) to make our patients chew their nitroglycerin tablets but still they mostly swallow them in water. It cannot be too strongly emphasized that glyceryl trinitrate tablets B.P., 1/130 grain (0.5 mg.), are *the* specific for angina and, used intelligently and often, they are a most effective means of treatment. Unfortunately the longer-acting nitrates ('peritrate', 'pentoxylon', *et al.*), widely advertised to prevent angina, are practically useless.

Intermittent claudication.—The vasodilator action of papaverine is sometimes utilized to treat ischæmic leg pain by means of intra-arterial injection. Efficacious and dramatic in its immediate effect, and of extreme value in incipient gangrene, there is difference of opinion as to its long-term use. Unfortunately, papaverine given by mouth (1 to 2 grains [60 to 120 mg.] thrice daily) has little effect, but some cases appear to benefit from it, although the drug occasionally causes loss of appetite. Numerous other vasodilators have their advocates but none is of proven efficacy, and in so variable a condition assessment is always difficult. 'Dilatal' probably has the virtue only of being up-to-date; the oral dosage is a test dose of 1 tablet (2.5 mg.). If this is well tolerated, 8 to 12 tablets daily, after meals.

Night cramps.—Calcium lactate, 10 to 15 grains (0.6 to 1 g.), or quinine sulphate, 3 grains (0.2 g.), taken at bedtime, often bring relief and a most grateful patient.

CENTRAL NERVOUS SYSTEM

Migraine.—As a preventive, Gowers' mixture still has no serious competitors and is of great value taken night and morning, well or ill, over a period of months. The formula advised is given below. (The solution of glyceryl trinitrate is liable to decompose if the mixture is kept more than a few days.)

Sodium phenobarbitone	¼ grain (16 mg.)
Solution of glyceryl trinitrate	1 minim (0.06 ml.)
Solution of strychnine hydrochloride B.P.	3 minims (0.2 ml.)
Tincture of gelsemium B.P.C.	7 minims (0.4 ml.)
Dilute hydrobromic acid	5 minims (0.3 ml.)
Chloroform water.....	to ½ fluid ounce (15 ml.)

For treatment of the attack ergotamine tartrate is widely recommended but few migraine patients actually seem to take it. Those who do, the real sufferers, usually learn to inject it early in an attack, subcutaneously or intramuscularly, in a dose of 0.5 to 1 mg. Orally the dose is 1 to 2 mg. repeated in an hour, but side-effects are common: vomiting, and muscle pains, particularly in the thighs, and I have once seen spasm of the saphenous vein which passed off in a few hours.

Two newer preparations in current use for migraine are 'cafergot' and

'migril'. 'Cafergot' (ergotamine, 1 mg., and caffeine, 100 mg., in each tablet) is given orally or by suppository and is claimed to be comparable in efficacy to parenteral ergotamine. 'Migril' contains ergotamine, 2 mg., caffeine, 100 mg., and cyclizine, 50 mg., in each tablet. Time will decide, but experience counsels use of the preparations *now* while they still may be effective.

Trigeminal neuralgia.—Many cases need alcoholic injection (either of the 3rd division or of the gasserian ganglion) or trigeminal root section, but some can be managed by simpler measures:

(i) *During the attack:* the inhalation of 15 to 20 drops of trichlorethylene vapour (vitrellæ of trichloroethylene B.P.C.). Tell the patient to lie down during the inhalation, which should not be repeated more than five times a day.

(ii) *For prevention,* the following mixture, particularly of use in mild cases and also in 'atypical facial neuralgia':—

Tincture of gelsemium	10 minims (0.6 ml.)
Phenobarbitone sodium	¼ grain (15 mg.)
Phenazone	5 grains (0.3 g.)
Codeine phosphate	¼ to ½ grain (15 to 20 mg.)
Syrup of orange	30 minims (2 ml.)
Chloroform water	to ½ fluid ounce (15 ml.)

To be taken three or four times a day half-an-hour before meals.

This mixture is also worth a trial to prevent the crises of tabes dorsalis.

Postherpetic neuralgia.—In mild cases the gelsemium mixture is useful. When more severe, one of the medium potency analgesics may be tried, but they may not work and there is great danger of addiction. Occasionally in the acute stage the following powder can be given for a few weeks:—

Aspirin	5 grains (0.3 g.)
Phenacetin	5 grains (0.3 g.)
Heroin	1/12 grain (5 mg.)

Dispense in a cachet. To be swallowed with water, 1 to 2 as necessary.

The cachet has the advantage that when the prescription is repeated the amount of heroin can be reduced without the patient's knowledge.

In chronic cases analgesics seem useless, and the patient often does better with a mild sedative: e.g. amylobarbitone sodium, 1 grain (60 mg.), or chlorpromazine; occupation and companionship are the best prescriptions of all.

RHEUMATOID ARTHRITIS

Cortisone.—In spite of the favourable M.R.C. reports on aspirin, in practice the big gun of cortisone is usually brought up sooner or later in long-standing cases. Experience so far suggests that for continued treatment it is best used along *with* aspirin. Restriction of the dose of cortisone to 50 mg. or, at the most, 75 mg. a day usually obviates œdema and other toxic effects. Oral cortisone certainly relieves pain and stiffness in the joints, but the painless perforation of a peptic ulcer is often fatal. Local hydrocortisone into single painful joints is also useful, and an improvement on earlier orthopædic needlings.

Phenylbutazone (*'butazolidin'*).—This flashed across the sky three or four years ago. There is no doubt that its immediate effect on painful joints is little short of miraculous, but relief is often not maintained and the drug is sometimes toxic to the bone marrow. Now much less frequently prescribed than formerly, it is of use in small doses (100 mg. twice daily), often in combination with other drugs. It also has a place in ankylosing spondylitis when simpler analgesics fail. Intermittent dosage is unwise as it may lead to sensitization but toxic effects are less likely to appear after four to six weeks of treatment.

GOUT

Colchicine tablet B.P.C. is specific for the attack (1/240 grain [0.25 mg.] = 15 minims [1 ml.] of tincture of colchicum) and is now preferred to the tincture. One tablet is given every hour for four to eight hours. Diarrhœa is an indication for reducing dosage. Aspirin helps many sufferers equally well. To prolong remissions a small dose (100 mg. twice daily) of phenylbutazone is sometimes effective—but so again is aspirin.

CHRONIC PAINS IN GERIATRIC PATIENTS

Old people often suffer from ill-defined pains—'fibrositis', 'neuritis' or 'neuralgia'—the scalp and the neck and back being particularly troublesome. When mobile, many are comforted by twice-weekly visits to that best of clubs, the physiotherapy department. Medicinally, Lord Horder's elegant prescription for effervescent aspirin is helpful and acts rapidly:—

Acetylsalicylic acid in powder	15 grains (1 g.)
Phenacetin powder	3 grains (0.2 g.)
Caffeine citrate effervescent powder	60 grains (4 g.)

Half to one powder taken in 1 fluid ounce (30 ml.) of water.

A hot bath and a whisky at bedtime are supporting measures and the addition of a teaspoonful of brandy to the powder does not go amiss.

The pain of osteoporosis in old people is greatly helped by 'mepilin' (ethinylœstradiol 0.01 mg., and methyltestosterone 3 mg.). The dose is 2 to 6 tablets daily.

HEADACHES AND OTHER PAINS ASSOCIATED WITH EMOTIONAL INSTABILITY

In these days when psychiatrists are overburdened with patients suffering from trivial complaints most of which ought to be treated by the family doctor, a little reassurance and one of the following will often side-track a six weeks' waiting list:—

(i) Gentian and alkali mixture with phenobarbitone N.F., ½ fluid ounce (15 ml.) thrice daily after food.

(ii) Potassium bromide and nux vomica mixture N.F., ½ fluid ounce (15 ml.) twice daily.

(iii) When neurosis is a marked feature, potassium bromide and valerian mixture N.F., ½ fluid ounce (15 ml.) twice daily.

(iv) A cube of 'sedebrol' (17 grains [1.1 g.] of sodium bromide) at night in water or soup. The ritual associated with unwrapping and dissolving the cube is beneficial.

The most up-to-date view is that bromides are less efficient than barbiturates. Potassium bromide can only act by displacing chloride and this takes at least a week to effect. Occasional dosage must therefore be useless, and it may be that (ii), (iii) and (iv) above should be discarded, but they seem to have been of use—and experts sometimes change their minds.

MISCELLANY

Some remedies are too often forgotten because of their simplicity. To mention only three: the kaolin poultice for pleuritic pain; the camphor liniment for sore chest muscles, and the inhalation (menthol and benzoin inhalation B.P.C.) for a blocked sinus.

The injection of a local anæsthetic (e.g. 2 per cent. procaine) into painful fibrositic and other nodules, real or imaginary, is safe enough for the enthusiastic amateur, but intravenous procaine for dressing painful burns requires professional anæsthetic skill. In paraphimosis, swelling is lessened by the injection in the 3 and 9 o'clock positions of a little of a solution containing 1000 units of hyaluronidase in 5 ml. of 1 per cent. procaine, ten minutes or so before reduction is attempted.

Pain in skin conditions.—The antihistaminics are of value and are dealt with by Dr. Allan Birch (see page 65). Other anæsthetic ointments or creams are dangerous because of sensitization dermatitis: 'the 'caines are banned'. In boils, dry heat is a better counter-irritant than fomentations, which produce a sodden, readily infected skin.

Drugs in childhood.—A pædiatrician makes the following observations:—

(1) Soluble aspirin (see page 34), Dover's powder, codeine, 'nepenthe', and morphine cover all eventualities.

(2) Dover's powder is excellent and should be used frequently for pain associated with febrile conditions. The dose at three months is $\frac{1}{8}$ grain (8 mg.) four times a day; at six months, $\frac{1}{4}$ grain (16 mg.) four times a day.

(3) Codeine phosphate, 1/64 grain (1 mg.) per lb. (2.2 mg. per kg.) body weight, subcutaneously, is often useful.

(4) The dose of 'nepenthe' is 1 minim (0.06 ml.) per year of age + 3 minims (0.2 ml.).

(5) The dose of morphine is 1/50 grain (1.3 mg.) per 10 lb. (4.5 kg.) of body weight. Morphine is *not* dangerous if given with regard to body weight.

SUMMARY

Essential analgesic drugs are few but frills are plentiful. For our desert island we could get on well with aspirin, pethidine and morphine and (for the ladies) that Liverpool benefaction to mankind, the famous Minnitt apparatus, safely administered by midwives for a generation and by its simplicity relieving countless thousands.

ANTACIDS

By A. H. DOUTHWAITE, M.D., F.R.C.P.
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ALTHOUGH we associate the use of antacids with the treatment of peptic, usually duodenal, ulceration, we should remember that the consumption of these drugs by individuals who have no organic disease takes place to an enormous extent.

THE 'OCCASIONAL DYSPEPTIC'

They are the persons who are subject to indigestion from time to time which, on analysis, proves to be a distension, or a feeling of distension, of the stomach after a meal. This sensation may be produced by overloading of the stomach, especially with fatty food, or it may be felt when there is no distension of the organ but when it is in a phase of high tone and hypermotility. This state is common in the hardworking perfectionist whose actual food intake is, if anything, on the small side. There is really no reason why we should deprecate occasional self-medication with one or other of the alkaline stomach powders or fruit salts which are offered to the public. They relieve the symptom with a belch and they do no harm.

Why it is that such comfort is obtained is by no means clear, though probably it is the evolution of gas rather than the temporary neutralization of acid which is beneficial. Radiological observations have shown that single therapeutic doses of alkali taken in this way have no effect on emptying rate and a negligible and transient antacid effect. Those preparations which result in rapid evolution of CO_2 produce for a few minutes distension of the stomach and even arrest of peristalsis, but the former state is soon regained yet the post-prandial discomfort may not recur. The immediate relief after eructation is well known but its explanation eludes us. It is relevant to note that air-swallowing is not always a neurosis. A discomfort from organic disease of the digestive system from gall-bladder to appendix commonly induces aerophagy and thus gastric distension and belching. It seems to be a fundamental reflex mechanism of unknown teleological significance.

The occasional dyspeptic then may be left to his carbonates and bicarbonates.

INDICATIONS FOR ANTACIDS

The choice of antacid and its method of administration is of great importance, however, in the treatment of disease. The conditions for which neutralization of gastric HCl is needed are œsophagitis, œsophageal benign ulcer, hiatus and paraœsophageal hernia on the one hand, and duodenal ulcer on the other. For gastric ulcer with normal or high acidity it is also desirable.

ŒSOPHAGEAL DISEASE

The œsophageal group of patients needs this protection because the gullet has no mucosal resistance to the erosive effect of hydrochloric acid. Heartburn is a warning signal of acid reflux into the œsophagus and this may occur repeatedly in persons who have developed a laxity of the cardia even though no hernia be demonstrable. At the other extreme we find hiatus hernia with peptic ulcer of the œsophagus and dysphagia, or paraœsophageal hernia with ulceration of the sac, anæmia, epigastric pain, and even severe hæmorrhage. This group are all subjected to increased hazards if HCl has free access to the unprotected surfaces.

The choice of antacid is of less importance perhaps than the form in which it is taken although further remarks on this matter will be made later when dealing with duodenal ulcer. Provided that the antacid is continuously flowing over the lower end of the œsophagus, it is likely to be effective. This is fully possible only for patients who are confined to bed. Such rest is in fact advisable for the first two weeks of treatment of œsophageal ulcer. A Ryle's tube should be passed through the nose into the gullet to about two inches above the cardia; the position should be confirmed by x-rays if available but failing this the tube markings must be relied upon. Milk, which is only a weak antacid and which protects mechanically, and aluminium hydroxide gel, ½ fluid ounce to one pint (15 ml. to 570 ml.), are mixed and given by slow drip; about twenty drops per minute day and night. Healing is rapid.

Subsequently neutralization is necessarily less continuous, but an approach to the ideal is provided by a slowly dissolving antacid tablet which is lodged between the gum and the cheek. Thus with each act of swallowing, alkali is carried down over the gullet to the stomach. It is remarkable how little is the quantity needed to depress effectively the concentration (pH) of gastric HCl. The first such tablet ('nulacin') advised in an endeavour to simulate the milk-alkali drip was composed of:

The compressed solids of whole milk ..	40 grains (2.6 g.)
Magnesium trisilicate.....	3.5 grains (0.23 g.)
Magnesium oxide	2 grains (0.12 g.)
Calcium carbonate	2 grains (0.12 g.)
Magnesium carbonate	0.5 grain (0.03 g.)

The neutralizing power to pH_4 is 3.5 mEq./g. The most active constituent is in fact the magnesium oxide. The milk basis acts not only as a convenient vehicle but also affords some protection of the lower œsophagus mechanically and this may be important. The rate of consumption should be two an hour to a maximum of sixteen a day. The danger of overdosage giving rise to alkalosis is very largely theoretical unless there is vomiting and renal function is depressed.

We are now left with the problem of the gullet unprotected at night and to this as yet we have no complete answer. Some degree of success can be achieved by using the following mixture:—

Bismuth oxycarbonate	.....	30 grains (2 g.)
Magnesium carbonate	.....	20 grains (1.3 g.)
Magnesium oxide	.....	10 grains (0.6 g.)
Mucilage of acacia	.....	q.s.
Water	..... to	½ fluid oz. (15 ml.)

This dose is taken at bedtime. The amount of mucilage of acacia required is sufficient to make a thick emulsion.

The purpose of the emulsion is to provide an alkaline and protective coating to the lower end of the œsophagus. If in addition the output of gastric acid during the night can be reduced, or its concentration lowered by means which will be described later, so much the better.

The use of antacids in these forms of œsophageal disease is of course only part of the general treatment, which lies outside the scope of this article and which relates to diet, posture and reduction of obesity when present.

DUODENAL ULCER

The difficult problem presented by patients with duodenal ulcer is that in the majority of cases the acid output is much higher in respect of volume and concentration than that of normal persons or of individuals with gastric ulcer. The secretion of gastric juice is reflex and depends upon stimulation either through nervous or hormonal channels directed to excite the secretory cells. The influence of anxiety and other nervous states can be understood as being mediated through the vagus and it is this pathway which serves psychic secretion. The main hormonal influence is derived from gastrin, but in the final mechanism the output must depend upon the response of the oxyntic cells of the stomach. The fact that patients with duodenal ulcer produce such a continuous outflow of highly acid gastric juice both day and night could be explained by an excess of one or other influence or on the possibility that the total number of secreting cells is exceptionally high. The work of Hunt and Kay (1954), using large doses of histamine which produce a maximal secretory response quite independent of nervous or hormonal influences, has proved that in persons with duodenal ulcer there is an increased maximal secretory capacity. The increase is something in the order of 70 per cent. It is of considerable interest to note that the basis for this remarkable state has been revealed by the histological studies of Cox (1952) who showed that in male patients with duodenal ulcer approximately 75 per cent. more parietal cells were present in the gastric mucosa than in normal individuals.

Whether this excess of cells is present from birth or whether it is induced by nervous and hormonal factors is not yet known but it seems probable that a work hyperplasia occurs for it has been shown by Hunt and Kay that, when duodenal stenosis arises from a duodenal ulcer, and when therefore there is increased work thrown on the stomach, the maximal secretory capacity is augmented.

In the treatment of duodenal ulcer with antacids an important point to bear in mind is that in the absence of stenosis the stomach may eject its contents very rapidly. It is for this reason that the occasional administration

of even large doses of alkali is valueless because the substance is thrown out of the stomach too quickly to be effective. Thus there is a temporary reduction of acid which can be of little value in aiding the process of healing. This has been repeatedly demonstrated by study of fractional test meals with various alkalis and antacids in normal and supranormal therapeutic quantities. It follows therefore that, once the acid has been secreted, the only effective treatment must depend upon the frequent addition of small amounts of antacid throughout the waking day. In short, the tablets in the mouth referred to in the earlier part of this article are infinitely to be preferred to doses spaced every two or three hours. On an empty stomach, or a stomach containing relatively non-stimulating food such as a gruel test meal, the 'nulacin' tablet could so raise the gastric pH, that is to say lower the acid concentration, as to produce an undesirable degree of alkalinity. When given, however, in the presence of ordinary mixed diet, this has been shown not to occur.

There is another preparation presented as a slowly dissolving tablet which is taken in exactly the same way. It contains aluminium glycinate with a small quantity of alkali and buffers the gastric acid without producing alkalinity. Aluminium hydroxide almost loses its activity on drying but, when combined with glycine, it forms a highly active suspension which quickly raises the pH to 4: this is effective therapy. Even when ten times the minimal effective dose is taken, the pH does not rise above 7. The condition of alkalosis does not arise when such a buffer is employed. Aluminium glycinate is marketed in a tablet called 'prodexin', which also contains a small amount of magnesium carbonate:—

Aluminium glycinate	0.9 g.
Light magnesium carbonate	0.1 g.

The neutralizing power to pH 4 is 4.6 mEq./g. It should be a rule to insist that all individuals suffering from peptic ulcer, and especially duodenal ulcer, should carry in the mouth between meals a tablet of 'nulacin' or of 'prodexin' to ensure protection of the ulcer between the periods when the acid is buffered by the food of the normal meals.

ION EXCHANGE RESIN

Considerable interest has been taken in the use of ion exchange resins, notably polyaminostyrene ('styrion') which has the ability to raise the pH, i.e. to reduce acidity. 'Styrion' is prepared in tablets of 0.4 g. and it is recommended that the tablets be chewed and swallowed. Neutralization of gastric acid converts the resin into the chloride form but when it passes into the alkaline contents of the small intestine it changes back into its original substance and is finally excreted unchanged in the fæces. It has been claimed that there is no disturbance of electrolyte balance and that there is no risk of alkalosis. The objection, however, still applies to the swallowing of powders or tablets, in that the stomach may eject too quickly

the antacid which is given. It is likely that the neutralizing power of this ion exchange resin—which is less than 1 mEq./g.—is mainly developed below pH 2 and, by neutralizing only as far as this, one may leave intact factors which normally operate the mechanisms which inhibit gastric secretion in response to the gastric contents. Against this, however, the neutralization does not seem to be effected over a sufficient range to be thoroughly satisfactory. We work with the hope of obtaining a pH in the region of 3.5 to 4, whereas a pH of 2 is in fact very acid. When speaking of pH it must be remembered that the increase of acidity, for instance between pH 2 and 1, is vastly greater than it is between, say, pH 5 and 4, or even 4 and 3. The ideal antacid would neutralize acid in the stomach to, say, pH 4 or even pH 5 and subsequently return the whole of the neutralized acid to the body. Experiments in progress at Guy's Hospital show that calcium carbonate is effective in this respect in that it may return to the body as much as four-fifths of the acid neutralized in the stomach.

The pepsin of the gastric juice can be inhibited in two ways: by raising the pH and by the action of special ions. Raising the pH to 4 abolishes more than half the peptic power of gastric juice, whilst aluminium ions are effective in still further reducing the activity which remains.

NOCTURNAL SECRETION

It will be seen that there are many considerations which have to be taken into account when choosing the right antacid. We can now claim to control gastric acidity adequately during the waking hours. As with œsophageal disease, so with duodenal ulcer, the night control is one of the utmost importance. Because the sucking of tablets is out of the question for the patient who is asleep, we have to devise some means of slowing the emptying of the stomach so that a large dose of suitable antacid will be retained for part, at any rate, of the night. If we gain three or four hours of neutralization, then the greater part of the twenty-four hours is covered. In that event there is reason to suppose that ulcers will not only heal more quickly but that relapse will be made far less likely.

PARASYMPATHOLYTIC DRUGS

This brings us to a consideration of the value of so-called parasympatholytic drugs which for this purpose we may regard as drugs inhibiting the action of the vagus. The use of belladonna is hallowed by tradition but for years the quantity employed was far too small to be of the slightest value. Generally it may be stated that none of the belladonna alkaloids, or hexamethonium, or tricyclamol chloride, or propantheline, can be regarded as true antacids, but they do reduce the *total* output of gastric juice. Their effect varies considerably from person to person, depending upon the amount of vagal activity in that individual. As, however, the concentration of the acid remains high, their use alone would be valueless; but in conjunction with antacids, by causing reduction of the total amount of acid to be neutralized, they

clearly enhance the action of the latter drugs. Another action which may be important is that they tend to slow the emptying of the stomach and certainly relax spasm which may be responsible at times for the pain associated with ulcer. It is therefore chiefly at night that we give them and in sufficient quantity to cause dryness of the mouth.

About 0.5 mg. of atropine sulphate, or 50 mg. of tricyclamol, or 30 to 45 mg. of propantheline, by mouth will be found to be about the correct dose for an adult. This should be taken at least half-an-hour before the administration of the final dose of antacid. It is not often now that we use hexamethonium but, if used, it should be given intramuscularly in a dose of 50 mg., followed by calcium carbonate, 3 g., and aluminium hydroxide gel, 15 ml., given together in a little water. If the patient can tolerate it, the simultaneous administration of 2 to 3 teaspoonfuls of olive oil will be of further value, for it not only tends to inhibit the output of gastric acid but also delays gastric emptying. When the patient wakes up in the middle of the night—as he so often does—the effect of the parasympatholytic drugs will probably have passed off. It will then be too disturbing to repeat the whole process but calcium carbonate and aluminium hydroxide in milk, already prepared at bedtime, should be taken.

ACID SECRETION

It may be of interest to review briefly some of the important points about acid secretion and the action of alkali in relation to the therapeutic problems involved. The acid secreted by the stomach arises from carbonic acid, the hydrogen ion of which goes into the stomach, the bicarbonate ion remaining in the blood. This means that the alkali reserve is temporarily raised. Usually the stomach passes the hydrogen ion into the duodenum and the pancreas secretes bicarbonate from the plasma so that the temporary rise in the plasma bicarbonate, i.e. the alkali reserve, is corrected, since both halves of the carbonic acid are now in the gut. If the hydrogen ions are neutralized in the stomach by an antacid, such as sodium bicarbonate, the bicarbonate of the pancreatic juice meets no acid and is reabsorbed so that the plasma bicarbonate is now raised. This promotes a secretion of less acid by the kidney and the alkali reserve returns to normal. If considerable quantities of sodium bicarbonate are taken, there is excess after neutralizing the gastric acid and this excess is absorbed almost completely.

The old belief that an acid rebound occurred after the use of bicarbonate is probably unfounded (Staffurth, 1953). In ordinary individuals, up to 150 g. of bicarbonate can be given by mouth daily and this dose is excreted by the kidneys although the plasma bicarbonate is raised during the period of administration. The important point which makes sodium bicarbonate a systemic antacid is that the excess is absorbed so that it would cause an increase in the alkali reserve even if the stomach did not secrete acid. On the other hand there are such antacids as calcium carbonate which are absorbed to a small extent. Thus calcium carbonate is available for neutraliza-

tion of the acid in the stomach where it is changed into calcium chloride and subsequently turned back into calcium carbonate in the gut, about 80 per cent. being excreted in the fæces unchanged.

SUPPRESSION OF HCl AT SOURCE

If we could find a drug which would arrest the formation of gastric HCl at its origin in the cells, this would be of much greater value than the employment of antacids neutralizing acid already poured out. Modern work is now directed towards this end. It has been shown, first by animal experiments and later in human beings, that it can be achieved to a considerable extent.

The investigations by Bond and Hunt (1956), later extended to patients in the hospital wards, revealed the remarkable fact that an organic mercurial, mersalyl, in small amounts, namely 0.1 g. in 250 ml. of 12 per cent. aqueous solution of glucose, will, when introduced into the stomach, inhibit the formation of acid. This effect lasts from two to two-and-a-half hours and is produced by rapid action, for if the fluid is withdrawn after some twenty minutes, the persistent anacidity is not influenced. In other words it seems that the mercury is in some way fixed to the oxyntic cells of the stomach for this length of time. The glucose is used largely in order to supply, in the first place, sufficient volume of fluid to bathe the whole of the interior of the stomach and secondly to delay the emptying of the stomach. Mersalyl can be taken by mouth in this way and a single dose at night will thus give from $2\frac{1}{2}$ to 3 hours of control of acidity. This virtually reduces the problem of nocturnal acidity to control of the second half of the night, that is to say the last $3\frac{1}{2}$ to 4 hours of sleep. It may be that this remnant is unimportant if twenty hours of the twenty-four are under control.

It seems likely that the mercurial inhibits a sulphydryl enzyme which normally takes part in the formation of gastric acid. The taste is not pleasant and in some susceptible individuals slight griping or loose stools may arise, but it is unlikely that a single dose at night, during the active stage of the disease, will do more than cause the mildest discomfort, and it is certain that it will largely suppress the acid at its source. Work with other metals and metalloids is naturally progressing in the hope of finding some even more lasting and less potentially toxic substance, but it must be emphasized that this form of mercury has nothing like the same toxicity as the inorganic forms.

The last difficulty in treatment with antacids is to induce the patients to cooperate so that when they have lost their pain they will continue to protect themselves by the simple measures described above.

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HÆMOPOIETIC DRUGS

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In any review of hæmopoietic drugs, iron must still take pride of place.

IRON

Iron is the oldest and the most widely used hæmopoietic drug. Its essential function is to correct a body deficiency which may have been brought about in various ways, and it is useless therapeutically unless such a deficiency exists.

Iron deficiency occurs as the result of three causes which, in the individual patient, may be operating independently or together. These are nutritional inadequacy of iron-containing foodstuffs, defective absorption from the alimentary tract, and loss of iron from the body by hæmorrhage which may be physiological or pathological. Most commonly, iron deficiency is seen in women of the child-bearing age whose dietary intake of iron is inadequate to compensate for the losses incidental to menstruation and childbirth.

Defective absorption is often associated with partial or complete lack of hydrochloric acid in the gastric juice. By itself achlorhydria does not necessarily result in iron deficiency since, with a liberal diet, sufficient iron can still be made available to preserve a normal balance. If, however, the diet is inadequate, or loss of blood is excessive, defective gastric function may well turn the scales adversely and result in iron deficiency. Less common causes of defective absorption of iron are gastric operations such as gastrectomy and gastroenterostomy, and intestinal malabsorption as, for example, in the sprue syndrome. Hæmorrhage from the alimentary tract must always be kept in mind as a possible cause of iron deficiency. Frequently it is not obvious, and revealed only when the stools are tested for the presence of occult blood. It is the commonest cause of iron deficiency in male patients, in whom nutritional inadequacy is relatively uncommon. It will be evident that medicinal iron may be curative in cases of iron deficiency due to malnutrition, but it can be no more than palliative in cases of severe malabsorption or persistent hæmorrhage.

The diagnosis of iron deficiency may be easy when the characteristic hypochromic blood picture is accompanied by clinical features such as koilonychia and glossitis, or a history of repeated pregnancies, but it must be borne in mind that a hypochromic anæmia is not always due to body iron deficiency. In toxic, infective, or cachectic states there may be interference with utilization of iron by the bone marrow resulting in anæmia similar morphologically to that seen in iron deficiency. In such cases diagnosis may necessitate examination of the bone marrow for free stainable iron,

which is usually abundant, and of the plasma for its iron-combining capacity, which is usually reduced. In true iron deficiency these findings are reversed. In this type of anæmia, since the failure is in utilization and not in supply, iron therapy is ineffective.

PREPARATIONS OF IRON

In the great majority of patients *oral therapy* still provides the most convenient and practicable method of administering iron. Ferrous sulphate, in 3-grain (0.2 g.) tablets thrice daily, is probably the most popular preparation. If it is preferred that iron be given in liquid form, the well-known ferric ammonium citrate, 30 grains (2 g.) in chloroform water three times a day, should be prescribed. To avoid staining the teeth it should be taken through a straw. Iron therapy sometimes induces gastro-intestinal disturbances. These may be minimized by giving the drug after meals, and by starting with doses about a third of the optimal and gradually increasing over several days. If intolerance persists, other preparations such as ferrous succinate or ferrous gluconate are worth trying.

There is some theoretical justification for augmenting iron with vitamin C, since it is believed to facilitate iron absorption; but unless the patient is suffering from a deficiency of this vitamin it is doubtful whether it is of much therapeutic value. Similarly, when achlorhydria is present, the administration of dilute hydrochloric acid is indicated on theoretical grounds, but its practical value is not very evident. In some patients, however, dyspeptic symptoms are alleviated by hydrochloric acid.

During recent years the *parenteral administration* of iron has become a practical proposition. The preparations of saccharated oxide of iron first available were suitable only for the intravenous route, but more recently an iron-dextran preparation has been marketed which can be given intramuscularly. Experience so far indicates that, in view of their lesser risk of toxic side-effects and of their facility in administration, the intramuscular preparations are to be preferred. Even with these, however, unfavourable reactions occasionally occur, and staining of the skin at the site of injection is not uncommon. Care must also be taken not to overdose, since excess of iron accumulates in the tissues and may lead to irreversible damage of the liver and other organs. Treatment should be instituted with a small dose, such as 25 mg. of iron in 1 ml. of solution, and increasing to 100 mg. daily. The total dosage required may be calculated on the basis of 25 mg. of iron being needed to restore 1 per cent. in the hæmoglobin level.

Iron therapy is not necessarily more effective given by the parenteral than by the oral route. A daily rise in the hæmoglobin level of 1 per cent. or more may be obtained by either route. In patients suffering from defective absorption, however, oral therapy may be less favourable. In general, the parenteral route should be reserved for the following categories of patients. Those with a genuine intolerance for oral iron, and these are very few; those who cannot be relied upon to take iron regularly; cases of anæmia due

to malabsorption; recent cases of hæmatemesis in which oral therapy might be injudicious; and finally patients, such as women in the later stages of pregnancy, in whom it is undesirable that there should be any uncertainty in the rapid restoration of the hæmoglobin level.

Iron therapy in the treatment of anæmia should, of course, be supplemented by general measures including the correction of defective diet and attention to any underlying causal factors. The administration of oral iron should be continued for about three months after the blood picture is restored to normality. In patients with defective absorption it may in some cases be necessary to continue to give iron, although in reduced dosage, indefinitely.

COPPER AND COBALT

These, and probably other trace elements, are necessary for hæmopoiesis, but the amounts required are so small that in human beings adequate supplies are almost invariably provided by the food, however defective it may be in other respects. In anæmic infants, however, it may be desirable to give small amounts of *copper* along with medicinal iron, but many commercial preparations of iron contain traces of copper.

During recent years isolated claims have been made for *cobalt* in the treatment of anæmias refractory to other forms of therapy, but these have not been widely confirmed and further information is necessary before its value can be evaluated. Cobalt should not be given indiscriminately since it is liable to cause gastro-intestinal disturbances, and goitrogenic effects have been ascribed to it. It should be noted that cobalt is present in cyanocobalamin but the hæmopoietic activity of this substance does not appear to be connected with the effects of the element itself.

LIVER EXTRACTS, CYANOCOBALAMIN, FOLIC ACID

Since these substances are used in the treatment of megaloblastic anæmias, they may conveniently be considered together.

Crude *liver* preparations, including whole liver, proteolysed liver, and liver extracts for oral administration, contain both cyanocobalamin and folic acid, but their content of these substances is relatively meagre and consequently their dosage needs to be high if they are to be effective hæmopoietically. Liver extracts suitable for parenteral administration contain cyanocobalamin, but only small traces of folic acid. The more highly refined extracts may contain as much as 10 micrograms of cyanocobalamin in each ml., whilst the cruder extracts contain appreciably less than this.

Although there has been much speculation about the possible existence of additional hæmopoietic factors in liver, there is no convincing evidence that there are any such factors which are of therapeutic significance. Consequently, cyanocobalamin and folic acid, since they have become widely available, are tending to supersede liver therapy, and are likely in the future to replace it entirely. Indeed, apart from the nutritive value of certain whole liver preparations given by mouth in cases of severe malnutrition, liver therapy is now difficult to justify.

In the treatment of Addisonian pernicious anæmia, which is by far the commonest type of megaloblastic anæmia encountered in temperate climates, *cyanocobalamin* is the drug of choice. It can conveniently and cheaply be given in quantities considerably exceeding those contained in feasible doses of liver extract, and is almost free from the risk of sensitization. It is now recognized that in pernicious anæmia there is a widespread tissue deficiency in cyanocobalamin, and that restoration of the patient to general health may be most rapidly ensured by generous dosage of the vitamin. No ill-effects have been observed to follow high dosage and, although there is some wastage through excretion in the urine, this is of no importance in view of the cheapness of the drug. It is therefore sound practice to administer 1000 micrograms of cyanocobalamin intramuscularly as soon as the diagnosis is properly established. This amount is available in a single millilitre ampoule. The dose may be repeated every two weeks until the patient's blood picture is restored to normal. This plan of treatment has the advantages of reliability, cheapness, and convenience both for doctor and patient; moreover it provides the safeguard of doing all that can be done to prevent neurological complications developing and to arrest them if they are already present.

For maintenance treatment an injection of 100 micrograms of cyanocobalamin at monthly intervals is usually regarded as adequate, but evidence is accumulating that satisfactory remission may be secured by doses of 1000 micrograms given every three months. If this procedure is adopted, however, it is desirable, until further experience has been obtained, that patients should continue to be seen every month.

It is generally appreciated that to ensure effectiveness in the treatment of pernicious anæmia, cyanocobalamin must be administered parenterally. It has recently been claimed, however, that satisfactory results can be obtained by the oral administration daily of pills containing cyanocobalamin along with a preparation containing intrinsic factor, usually obtained from hog's duodenal mucosa. This form of treatment has been assessed in a fairly large series of patients in my clinic over a period of more than two years. Although the majority of the patients showed reasonably good initial responses to the treatment, an unacceptably high proportion of them failed to maintain satisfactory blood levels during maintenance treatment. Accordingly, this treatment has now been abandoned and replaced by parenteral therapy. Apart from all other considerations, oral therapy has the inevitable drawback that the onus for taking the drug rests on the patient; and not all patients can be convinced, when in therapeutic remission, that they can remain well only by regular maintenance therapy.

It is universally agreed that *folic acid* has no place in the treatment of Addisonian pernicious anæmia. Although it may produce a variable degree of hæmatological remission, it fails to prevent neurological involvement, and, indeed, may hasten its onset.

Non-Addisonian megaloblastic anæmias are relatively rare in this country, but it is important to remember that some cases may be due primarily to

lack of cyanocobalamin, others to lack of folic acid, and some to lack of both. If the major deficiency is in folic acid, treatment with cyanocobalamin or refined liver extracts will be ineffectual. Megaloblastic anæmia of pregnancy as seen in this country is usually highly responsive to folic acid given daily by mouth in 10-mg. tablets. Crude liver preparations by mouth may also be effective, but cyanocobalamin or refined liver extracts are useless in most cases. In the megaloblastic anæmia due to malnutrition, or to malabsorption, whether caused by the sprue syndrome or by structural abnormalities of the alimentary tract, the therapeutic requirements vary. In some cases, good results may be obtained with cyanocobalamin alone, in others with folic acid; not uncommonly a deficiency of both factors is present. Megaloblastic anæmia in infants is usually due to a folic acid lack, and responds to treatment with that substance.

In conclusion to this section, the reader may be reminded that it is only the megaloblastic anæmias which respond to cyanocobalamin or folic acid, and that not all macrocytic anæmias are megaloblastic. Consequently it is essential that a competent hæmatological diagnosis be established before treatment is instituted.

OTHER VITAMINS

Apart from cyanocobalamin and folic acid, vitamin C is probably the only vitamin of hæmopoietic activity having a place in practical therapeutics. In scurvy the anæmia is often primarily due to iron deficiency and requires therapeutic iron for its alleviation, but in some cases a satisfactory hæmatological recovery may occur with vitamin C alone. In certain rare cases of megaloblastic anæmia, deficiency in vitamin C has been shown to play a part in the underlying etiological mechanism, but this is mainly of academic interest.

In states of malnutrition or malabsorption, of course, the anæmia is often complicated by clinical syndromes due to various vitamin and other deficiencies which require appropriate treatment to supplement the specific anti-anæmic therapy.

HORMONES

Clinical experience has shown that various endocrine disorders are commonly associated with dyshæmopoiesis, but little evidence has emerged to support the view that hormones act specifically as hæmopoietic agents. For example, the anæmia that often accompanies myxœdema may respond to thyroid medication, but it is believed that this effect is due to the general stimulation of tissue metabolism rather than to a specific effect upon the bone marrow.

Since the advent of *cortisone* and *corticotrophin* much attention has been paid to their effect upon hæmopoiesis and to their therapeutic value in blood diseases. The present position may be summarized by stating that, although these hormones exert some influence on the blood-forming tissues, their main value in hæmatology is believed to depend upon their effect on the

underlying antigen-antibody reactions in certain hæmatological disorders.

The most gratifying therapeutic results have been obtained in acquired hæmolytic anæmias, especially in so-called idiopathic cases with a positive Coombs test or other evidence of an abnormal antibody reaction. A substantial degree of remission may be expected within two or three weeks in the majority of cases belonging to this group. In some cases the remission will be permanent after discontinuing the treatment. In others splenectomy may be necessary to obtain permanent remission, and in these hormone therapy may provide a valuable preoperative measure. In patients who, for various reasons, are considered unsuitable for splenectomy, permanent maintenance treatment with hormones may be necessary. Hormone therapy is of no value in congenital acholuric jaundice, or in other forms of hereditary hæmolytic anæmia.

Idiopathic thrombocytopenic purpura resembles acquired hæmolytic anæmia in its response to hormone therapy. In a high proportion of cases treatment is followed by symptomatic improvement and the bleeding stops or is reduced, although this may not be accompanied by a commensurate rise in the platelet count. Here again the duration of the response is variable. If a course of hormone treatment is not followed by permanent remission, the choice lies between splenectomy and permanent maintenance therapy.

Of other blood diseases amenable to hormone therapy, the most important are acute leukæmias. Children are more likely to benefit than adults, and lymphoblastic leukæmia is more frequently responsive than other types. The results, however, are always unpredictable, and even in favourable cases unlikely to be of more than a few weeks', or at most months', duration.

Preparations.—Cortisone is generally used in preference to corticotrophin since it can be given by mouth. Dosage of cortisone acetate should be 200 to 300 mg. daily for adults, and 100 to 200 mg. for children. It should be given in divided doses at intervals not greater than six hours. Prednisone, a synthetic analogue of cortisone, 40 mg. daily in divided doses, appears to be equally efficacious and is less prone to promote fluid retention.

Corticotrophin should be given periodically as a temporary substitute for cortisone in patients receiving cortisone therapy over prolonged periods in order to obviate the risk of adrenal atrophy. It is also used to 'taper off' with on withdrawing cortisone. The dosage is 80 to 200 mg. daily, and it must be injected intramuscularly, in divided doses six-hourly. There is, however, a long-acting preparation available in gel form which need be given only once daily.

The employment of these hormones in hæmatology, needless to say, is governed by the usual precautions and contraindications.

CYTOTOXIC DRUGS

Although the term, hæmopoietic drug, is generally understood to imply a substance which stimulates blood formation, the various cytotoxic substances now employed in the palliative treatment of leukæmia and allied

conditions probably merit inclusion under this heading because of the favourable effect that they exert indirectly on hæmopoiesis in responsive cases. Because they are all potentially highly dangerous, and are mostly still in the experimental stage, these drugs should be employed only under expert supervision. In this article therefore only a brief outline will be given of the therapeutic status of some of the better known of these compounds.

Nitrogen mustard has been employed in the treatment of Hodgkin's disease and other reticuloses, chronic myeloid and lymphatic leukæmia, and polycythæmia vera. It is, however, highly doubtful whether it is as effective as irradiation or other chemotherapeutic drugs. It is usually given as di(2-chloroethyl) methylamine hydrochloride (mustine) when it must be administered intravenously in saline. There is also a preparation 'TEM', *triethylene melamine*, which is suitable for oral administration. These drugs cause cell death during the phase of mitosis.

Busulphan ('*myleran*'), which has been more recently introduced, has an action similar to that of the mustards. It promises to be of real value in the control of chronic myeloid leukæmia, and may prove superior to any existing alternatives. It is available commercially in tablet form and is given by mouth. As with all these drugs, overdosage may result in bone marrow aplasia. Hence great caution and strict hæmatological control are essential.

Demecolcine ('*colcemid*'), a derivative of colchicine which has long been known to inhibit mitosis, has recently been claimed to be effective in chronic myeloid leukæmia, but it has not yet been adequately evaluated.

Urethane has been used in the treatment of chronic myeloid leukæmia for a number of years, but it is probably less effective than busulphan and is more apt to produce nausea and vomiting. It is also sometimes of palliative value in multiple myelomatosis. It is usually given orally in fluid form. It is a general cell poison but its exact mode of action is uncertain.

Mercaptopurine ('*puri-nethol*') is of value in the palliation of acute leukæmias of all types, and results in complete or partial remissions lasting for a few weeks or months in about 25 per cent. of all cases, although children are more responsive than adults. The drug is available in tablet form, being given by mouth. It inhibits cellular activity by interfering with nucleic acid synthesis.

'*Aminopterin*' is also effective in acute leukæmias, but usually only in young children. It is very apt, however, to produce severe toxic effects, especially in the alimentary tract. It is on the whole inferior to mercaptopurine and cortisone, and should be used only in cases which have failed, or ceased, to respond to either of these drugs. It belongs to the group of folic-acid antagonists, blocking the conversion of folic acid to folinic acid and thus inhibiting nucleic acid synthesis.

In all patients with acute leukæmia who are severely ill, cortisone is the drug of choice in the first instance. It should be appreciated, however, that at the best only temporary remission can be hoped for with any form of therapy at present available.

HYPOTENSIVE DRUGS

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SYSTEMIC arterial pressure when unduly raised is remarkably sensitive to starvation, pyrexia, venesection, lumbo-dorsal sympathectomy and a variety of drugs. It is this volatility which makes initial treatment promising but continuous control profoundly difficult. No one method is wholly satisfactory, each new drug or combination of drugs being claimed as an advance. It behoves us therefore to consider what benefit may be expected from lowering the blood pressure and to offset this against the inconvenience and social disruption entailed by adequate hypotensive therapy.

INDICATIONS FOR HYPOTENSIVE DRUGS

The mortality rates of insurance companies are evidence that raised diastolic pressure is associated with diminished life expectancy and particularly is this so in men.

Leishman (1953) observed 151 hypertensives under sixty years of age for two-and-a-half to five years, during which the death rate was 34 per cent. (51) and in men alone 44 per cent.

Unfortunately it is difficult to decide between hypertension and arterial disease as the cause of death, for the two are not synonymous. By arterial disease, I mean particularly atheroma and medial degeneration of the larger arteries, rather than medial hypertrophy of the muscular arteries and hyalinization of the intima of the small vessels, which are presumably the results of the high arterial pressure.

Bechgaard (1946) gives the cause of death in 293 patients with essential hypertension as 45 per cent. from heart disease, 16 per cent. from cerebral apoplexy, 10 per cent. from uræmia and 29 per cent. from intercurrent disease.

Pickering (1955) has adduced good evidence that there is no such entity as 'essential hypertension', that there is no dividing line between normality and hypertension and that the important factors are inheritance and environment. In so far as this stays the search for a specific cause the hypothesis is helpful. Yet we remain ignorant of the precise mechanism by which the diastolic pressure is persistently raised in all conditions except chromaffinoma. Even with the removal of such a tumour the arterial pressure does not always return to normal. A similar occurrence may be noted after the surgical treatment of coarctation of the aorta.

There is therefore some justification for treating moderately raised blood pressure in the hope of avoiding progressive change. In malignant hypertension there is no doubt that the height of the arterial pressure and the speed with which it has reached this level are the determining factors in the fibrinoid necrosis of arterioles, and that lowering of the blood pressure alone

will arrest this process if undertaken sufficiently early. Any considerable delay in treatment may allow irreparable renal damage and favour termination in uræmia. Other obvious benefits of a lowered blood pressure in hypertension are the recovery from left ventricular failure, and the disappearance of encephalopathy and morning headache. Whether the frequency of cerebral thrombosis or of coronary thrombosis is increased will remain difficult of proof.

These then are, in my opinion, the indications for treatment with hypotensive drugs:—

(i) The malignant phase or the threat of its occurrence (a rapidly rising diastolic level particularly under 45 years and where there is not a removable cause).

(ii) Hypertensive left ventricular failure.

(iii) Hypertensive encephalopathy.

THE CHOICE OF DRUGS

The ideal hypotensive drug should be consistently effective by mouth with a period of activity of about eight hours and be free from side-effects. No such drug is currently available. The hypotensive drugs may be grouped into:—

(a) Those with mainly central action: 1-hydrazinophthalazine, dihydrogenated ergot, veratrum viride, thiocyanate and Rauwolfia serpentina.

(b) Those with a peripheral effect: dibenamine, benzylimidazoline and phentolamine.

(c) Those blocking ganglionic transmission: tetraethylammonium, pentamethonium, hexamethonium, pentapyrrolidinium, 'ecolid' and mecamylamine.

From this list we can exclude the anti-adrenaline substances, dibenamine, benzylimidazoline (tolazoline) and phentolamine, as unsuitable hypotensives. Tolazoline and phentolamine are used as a vasodilator and as a test of circulating noradrenaline, respectively. Thiocyanates are erratic in action and need frequent estimation of the blood level, which must be maintained between 8 and 12 mg. per 100 ml.; their use is not practicable out of hospital. Similar toxic effects occur with sodium nitroprusside: i.e. rashes, anorexia, drowsiness and confusion. Dihydrogenated ergot is theoretically an admirable drug producing vasodilatation of central origin, bradycardia and sedation; unfortunately tolerance is rapidly developed and the duration of effectiveness is short.

HYDRALLAZINE

(1-HYDRAZINOPHTHALAZINE. 'APRESOLINE')

Gross, Druey and Meier (1950) have described the hypotensive action of 1-hydrazinophthalazine and Reubi (1950) the accompanying increased renal flow. This latter is without change in the glomerular filtration rate and is less than proportionate to a raised cardiac output, from increased stroke volume and tachycardia. The drug inhibits humoral pressor agents such as

pherentasin and hypertensin. Partial tolerance to hydrallazine is rapidly acquired. The initial dosage is 12.5 mg. four times daily after food, gradually increasing to 50 mg. four times daily by the end of the second week and double this by the end of a month, depending upon the hypotensive response. Higher dosage is often used. Angina pectoris during treatment was noted by Harris and Turner (1954); headache and weakness have been transitory symptoms. With high dosage during six months a syndrome similar to disseminated lupus erythematosus has been reported (Morrow *et al.*, 1953); the signs rapidly regressed with the cessation of hydrallazine.

Although the initial response has been promising, prolonged treatment has not been satisfactory and it is now more usual to give hydrallazine in conjunction with rauwolfia, hexamethonium or pentapyrrolidinium. Rauwolfia is given in the form of reserpine, 1.5 to 2 mg. daily in divided doses for two weeks, and then the hydrallazine is added, starting with 100 mg. a day and gradually increased if necessary. Alternatively, hexamethonium chloride is given orally eight-hourly then the hydrallazine added and gradually increased. Schroeder *et al.* (1953) in particular have used this method with success. It has the dangers inherent in oral hexamethonium.

VERATRUM VIRIDE ('VERILOID')

The hypotensive effect of veratrum viride was described by Douthwaite (1928). It was subsequently used in puerperal eclampsia (Bryant, 1935), but its more general oral use awaited the preparation of standardized, stable, reproducible mixtures of the ester alkaloids. Veratrum produces hypotension, bradycardia and emesis; its action is on the central nervous system and vagal endings. Most of the arteriolar dilatation is central in origin and in practice the von Bezold reflex is of slight importance. The bradycardia is abolished by atropine without return of the blood pressure to its former level.

'Veriloid' is given in a dose of 4 mg. thrice daily after food, with an interval of not less than 4½ hours between doses. Should nausea or vomiting arise, the patient is told to lie flat and, if the symptom persists for more than half-an-hour, to halve the subsequent dose. After four days the first and last doses are, if necessary, raised and then the mid-day dose, to a daily total of 24 mg. With such a regime the blood pressure may be lowered in two-thirds of cases (Kauntze and Trounce, 1951); yet in half of these, toxic symptoms are an insuperable bar, although phenobarbitone is of some assistance. This leaves about a quarter in whom 'veriloid' is an adequate hypotensive agent. Review of such patients after 3½ years showed the survivors either changed to parenteral hexamethonium or with blood pressures which appeared relatively static (although not normotensive) without treatment. The only patients who seemed to respond well to 'veriloid' were those whose hypertension was not of a rapidly progressive type. The toxic effects of veratrum, even with the pure alkaloid germitrine, are inseparable from its hypotensive activities.

In 1953, Ford and Moyer reported the synergistic action of hexamethonium with Rauwolfia serpentina ('rauwiloid'). Dr. Joiner and I (1954) studied the effect of Rauwolfia serpentina in cases of severe hypertension already under treatment with veratrum viride; we found bradycardia and in certain patients lowering of the diastolic pressure, but no striking additive or synergistic action and no particular tranquillity such as has been claimed.

RAUWOLFIA SERPENTINA (RESERPINE)

Rauwolfia serpentina, prepared from an Indian shrub, has, like veratrum, been used for a variety of ailments. Vakil (1940) remarked favourably on its effect in hypertension. Subsequent reports stressed the hypotension, bradycardia and unique emotional calm with only minor side-effects (Arnold and Bock, 1953). Tolerance did not occur and dosage was simple. Doyle and Smirk (1954), with large doses of reserpine (2 to 3 mg. three times daily), noted remarkable falls of diastolic pressure (more than 45 mm. Hg in 7 of 20 patients); nasal and conjunctival congestion, flushing, somnolence, fatigue and depression were troublesome. Postural hypotension was rarely noted. In my hands the effect of 1.5 to 2 mg. reserpine has been rather unpredictable. Minor depression may occur with such a dosage but is rarely severe. The combination with methyl plenidate is said to counteract this.

When there is no urgency, treatment may be with reserpine, 1.5 mg. daily, increasing the dose short of side-effects; hydrallazine is then added in graded dosage. Alternatively, and in my opinion preferably, reserpine may be combined with pentolinium, 20 mg. half-an-hour before breakfast and twelve hours later. The dose of pentolinium is then gradually increased according to the response, as detailed by Smirk *et al.* (1954). The blood pressure is rendered more stable, adjustment of dosage is easier and the side-effects from parasympathetic paresis are less with such a combination.

Other additions to rauwolfia are protoveratrine and phenoxybenzamine in fixed ratio, based on the assumption of multiple etiology (Smith *et al.*, 1955).

METHONIUM COMPOUNDS

The pharmacology of the methonium salts was described by Paton and Zaimis (1948) and their circulatory effects by Arnold *et al.* (1949). These are the most potent hypotensive agents available, blocking both sympathetic and parasympathetic transmission through the ganglia, probably by combination with a receptor substance. The degree of parasympathetic paralysis varies with the particular compound, but it is never sufficiently in abeyance not to cause some side-effect. Hypotension is the outcome of peripheral and splanchnic vasodilatation and is associated with the upright position; the hypotension and the compensatory tachycardia can be lessened by the use of abdominal binders and bandages. In the recumbent position the cardiac output is diminished. Coronary flow is unimpaired and renal blood flow returns to normal after a preliminary decrease.

HEXAMETHONIUM

Hexamethonium bromide is more readily absorbed from the gut than the chloride or bitartrate, but the rate of absorption, even with meticulous care in dosage, is profoundly variable. Interference with parasympathetic transmission may produce ileus, which allows continuing absorption of the drug and, when gross hypotension is already present, may culminate in disaster, in spite of continuous noradrenaline intravenously. Laparotomy has been performed on account of such intestinal 'obstruction'. Pyloric obstruction may be precipitated by oral hexamethonium bromide. Finally, there is the danger of bromism, particularly when salt in the diet is restricted. Subcutaneous injection, however, in the absence of peripheral circulatory failure, ensures absorption and yields its effect from one to four hours after injection. The inception of such treatment entails admission to hospital.

During the usual investigation of heart and kidneys blood pressures are recorded four times daily for a control period. A test dose of 25 mg. hexamethonium chloride or bromide is then given intravenously and the patient's response in recumbent and erect blood pressures is recorded. If the response is trivial, 50 mg. is given on the following day. From such observations the patient's suitability and the necessary subcutaneous dosage are assessed. Usually a start is made with 25 mg. subcutaneously at eight-hourly intervals and this is increased as tolerance develops until the diastolic pressure is 100 to 110 mm. Hg in the erect position three hours after injection. This means that the patient will almost certainly need to lie down thirty minutes or so after each injection, but should in general be propped up or ambulant to benefit from the orthostatic hypotension. Within a month dosage should be fairly stable, but may be as high as 250 mg. thrice daily. During this time the patient learns to give the injections himself. Checks are made at monthly intervals; these may be made by his doctor or may entail attendance at hospital. In the absence of such supervision, recurrent hypotensive symptoms are the only guide to adequacy of dosage. In our experience, although control in hospital was often fairly good, outpatient supervision was unsatisfactory.

PENTOLINIUM TARTRATE ('ANSOLYSEN')

Like hexamethonium, pentolinium inhibits transmission between the pre- and post-ganglionic neurones of the autonomic nervous system. It is, however, preferable on account of its longer action and it has at least six times the activity of hexamethonium on sympathetic vasomotor tone. The pharmacology has been studied by Wien and Mason (1953) and its clinical use reported by Smirk (1953). Although pentolinium can be administered orally, the vagaries of intestinal absorption make any sustained control of the hypertension impossible unless combined with reserpine. When there is no urgency, treatment should begin with reserpine, 0.5 mg. twice daily for two weeks. Pentolinium, 20 mg., is then given half-an-hour before breakfast

and twelve hours later. Daily increments of 20 mg. are made to the morning and evening doses until there is slight faintness on standing two to three hours after ingestion. The development of tolerance will soon remedy this, but subsequent additions of pentolinium should be at progressively longer intervals until the diastolic blood pressure erect is around 100 mm. Hg. The individual doses may differ in amount or their spacing may be less, again depending upon the blood pressure readings. Meanwhile the reserpine is continued. Such a combination undoubtedly irons out the hypertensive peaks, but is often unsuccessful. When pentolinium is taken orally the bowels must be evacuated daily, and a regular aperient gives a margin of safety. Constipation means temporary but immediate cessation of treatment. Enemas should be avoided.

Whereas the success of oral pentolinium, even with reserpine, is speculative, by subcutaneous injection it is in my opinion the drug of choice. Starting with 2.5 mg. at 8 a.m., the afternoon dose should be less, for the effect of pentolinium persists up to six hours, and the evening dose larger. The amounts are gradually increased, and if necessary the intervals reduced, until the diastolic pressure is persistently below 120 mm. Hg and standing not lower than 80 mm. Hg: this is difficult to achieve without side-effects. Reserpine, 0.5 mg., is given orally twice daily; the dosage of pentolinium will concurrently need some reduction. The initial treatment must be in hospital, for the blood pressure must be recorded hourly: either erect, or sitting if the patient is confined to bed. The patient should be ambulant if possible and this requires constant medical supervision and a full explanation of the nature of hypotension. Subsequently, whether the treatment is subcutaneous or oral, the patient's condition is reassessed at weekly and, later, monthly intervals. This can only be undertaken satisfactorily in a special clinic.

SIDE-EFFECTS OF METHONIUM COMPOUNDS

Temporary undue hypotension occurs in all patients, particularly when vasodilatation from exertion, fever and hot weather or sodium depletion are additional factors; lowering of the head is usually sufficient remedy. Intestinal delay with absorption of an excessive amount of pentolinium will need treatment with intravenous noradrenaline. Paralysis of accommodation is usual, but a source of varying complaint. Spectacles may be helpful as may eserine drops. Dryness of the mouth—another example of parasympathetic blockade—tends to lessen under continuing treatment. Chewing-gum and lemon may alleviate the symptom; pilocarpine and carbachol have also been used. Diminution of libido is common and probably beneficial. Previously symptomless prostatic hypertrophy or pyloric stenosis or glaucoma may become prominent and necessitate the abandonment of treatment.

Beaven and Murphy (1956) have reported that nine of 44 hypertensive patients examined at necropsy after treatment with hexamethonium or

pentolinium had dissecting aneurysms of the aorta. This incidence is higher than would be expected in regard to the hypertension. Perhaps the considerable daily excursions of blood pressure are the important factor when medial degeneration is already present.

RESULTS WITH METHONIUM COMPOUNDS

The prognosis of the *malignant* phase of hypertension has been remarkably altered first by sympathectomy and later by the methonium compounds. Untreated survival was rarely longer than eighteen months. McMichael (1955) reports that of 32 patients treated with methonium, 43 per cent. survived for two years, compared with 7 per cent. of 30 untreated patients. There is no doubt that malignant hypertension, either primary or symptomatic, needs urgent treatment, for renal damage is rapidly progressive and cumulative. Adequate lowering of arterial pressure alone is sufficient to convert the condition to the benign phase. Similarly, pulmonary œdema and cardiac asthma from hypertensive left ventricular failure and hypertensive encephalopathy, including puerperal eclampsia, are amenable to hypotensive measures. Sufficient and sustained lowering of the diastolic blood pressure to below 100 mm. Hg can best be assured by injection of pentolinium. Although reserpine may be added treatment should be parenteral until the retinal changes are reversed or other symptoms adequately controlled. Later, if desired, a change to the oral route may be attempted, but I have found this rather unsatisfactory.

In a less urgent category are patients with progressively increasing blood pressures. A diastolic level of 140 mm. Hg is an approximate upper limit in those under 45 years. The retinal appearances may, however, be all-important, for the rather large fluffy exudates of retinal œdema may anticipate the bilateral papillœdema of the malignant phase, as emphasized by Pickering (1955). Such exudate is prognostically different from the 'hard' ischæmic exudate of retinal arteriosclerosis. Much slighter elevation of diastolic pressure warrants treatment during the later stages of pregnancy. Initial treatment should be with reserpine and then pentolinium orally. If control is inadequate subcutaneous injections must be used.

Satisfactory treatment entails very real discomforts. It is for this reason that the indications for treatment with hypotensive drugs should be clear-cut and the prognosis grave. 'Static' hypertension in the fat and elderly, and neurotic headaches require other measures.

Certain patients cannot be controlled by parenteral pentolinium or a combination of drugs and where renal damage has been minimal I have occasionally advised lumbo-dorsal sympathectomy and subsequently reinforcement with hypotensive drugs. Some patients will not tolerate the handicap of daily injections, and again sympathectomy must be considered. In one patient with uncontrollable hypertension and a previous sympathectomy, angina decubitus became so severe that bilateral adrenalectomy was performed with some success.

'ECOLID' AND MECAMYLAMINE

'*Ecolid*'(4:5:6:7-tetrachloro-2-(2-dimethylaminoethyl)-*iso*-indolinedimethochloride), although ganglion-blocking either by mouth or injection, differs structurally from hexamethonium and pentolinium. Its potency and effective duration are greater than those of pentolinium (Maxwell and Howie, 1955); the side-effects are similar. It seems that some patients respond better to 'ecolid', others to pentolinium (Smirk and Hamilton, 1956). I have had no personal experience of the drug.

Mecamylamine is a secondary amine which is well absorbed from the gut, but with a surprisingly slow excretion, 60 to 80 per cent. eventually appearing in the urine. With a single intravenous dose, 95 per cent. has been recovered from the urine (Allanby and Trounce, 1956). The hypotensive action from oral administration lasts twelve to twenty-four hours according to Moyer *et al.* (1955), whose preliminary report is encouraging. Allanby and Trounce (1956), however, have found a high proportion of side-effects. The use of the drug is still in the experimental stage.

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ANTIHISTAMINE PREPARATIONS

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MANY practitioners find these drugs difficult to understand because the number available is bewildering, and the response to them of conditions they regard as allergic is variable. Over 36 chemical compounds with antihistamine activity are on the market, but attention will be directed here to the 17 or so of them easily obtainable in Great Britain.

SOME GENERAL CONSIDERATIONS

Although adrenaline produces effects in the body opposite to those of histamine, and is useful in the treatment of some acute allergic conditions, it is not generally included among the antihistamine drugs. These are all chemical compounds—acid salts of basic amines existing as white powders freely soluble in water. They have been shown to alleviate histamine shock in guinea-pigs, and to inhibit the weal and flare produced in the skin by histamine. In addition to antagonizing histamine they have other useful actions, particularly on the central nervous system. As the degree of sedation is usually the deciding factor in which preparation to use a simple classification into three groups based on the sedative effect is offered in table 1. It will be seen that most preparations have only slight sedative effects and are in group I. The drugs in group III also cause peripheral side-effects, such as dry mouth and blurred vision, similar to those of hyoscine. So far only two antihistamines have been included in the *British Pharmacopœia:* mepyramine maleate and promethazine hydrochloride.

Although in the enormous literature on antihistamine drugs, indications for their use in almost all diseases will be found, it is in the symptomatic relief of allergic disorders that they find their chief place. Of these the ones due to 'extrinsic' histamine (urticaria and vasomotor rhinitis) are more responsive than those due to 'intrinsic' histamine (asthma) where the effect of histamine is produced directly in the tissue where it is released. Antihistamines are really blocking drugs, acting by competing with histamine and preventing its access to cells. The antagonism is not chemical or physiological (like that of adrenaline).

Which antihistamine to use in a given case is a difficult problem and as the individual response is apt to vary, it is often a question of trial and error. Unfortunately there is no close correlation between the effectiveness of any antihistamine drug as studied in the laboratory and its effect when used clinically. It is best therefore for the practitioner to choose one preparation from each group, and having become familiar with it to stick to it. Often the patient knows which preparation suits him best, and it is wise to continue with this one.

Practitioners are reminded that antihistamine drugs are Schedule IV poisons. Prescriptions for them must show the name and address of the patient, the total quantity of the drug or preparation to be supplied, the date

Approved name	Proprietary name and maker	Preparation	Colour and coating of tablets	Marking
GROUP I. Least Sedative				
Triprolidine	Actidil (Burroughs Wellcome)	2.5-mg. tablets Elixir 1 mg. in 4 ml.	White uncoated	Tabloid brand
Antazoline	Antistin (Ciba)	100-mg. tablets 2-ml. ampoules (100 mg.) 2% cream	White uncoated	—
	Ben-hist (Bencard)	100-mg. tablets	White	Bencard
	Histostab (Boots)	100-mg. tablets 2-ml. ampoules (100 mg.) 2% cream	White uncoated	—
Chlorcyclizine	Diparalene (Abbott)	25- and 50-mg. tablets 2% cream	Orange varnished	A
	Histantin (Burroughs Wellcome)	50-mg. tablets	White sugar-coated	—
Phenindamine	Ancolan (British Drug Houses)	25-mg. tablets	White uncoated	—
	Thephorin (Roche)	25-mg. tablets 5% cream	Yellow sugar-coated	—
Buclizine	Vibazine (Pfizer)	25-mg. tablets	White uncoated	—
Halopyramine	Synopen (Geigy)	25-mg. tablets	White sugar-coated	—
Chlorpheniramine	Piriton (Allen and Hanburys)	4-mg. tablets 1-ml. ampoules (10 mg.) Syrup 2 mg. per teaspoonful	Yellow uncoated	A H
GROUP II. Moderately Sedative				
Mepyramine	Anthisan (May & Baker)	50- and 100-mg. tablets 2-ml. ampoules (50 mg.) 2% cream Elixir 25 mg. in 4 ml.	Green sugar-coated	—
Tripelennamine	Pyribenzamine (Ciba)	50-mg. tablets Elixir 5 mg. per ml.	Blue uncoated	Ciba
Promethazine chlorotheophyllinate	Avomine (May & Baker)	25-mg. tablets	White uncoated	Avomine
Bromazine	Ambodryl (Parke Davis)	25-mg. capsules Elixir 10 mg. in 4 ml.	Pink with deeper pink band	
Dimenhydrinate	Dramamine (Searle)	50-mg. tablets	Yellow uncoated	Searle
GROUP III. Highly Sedative				
Diphenhydramine	Benadryl (Parke Davis)	25- and 50-mg. capsules 25-mg. tablets Elixir 10 mg. in 4 ml. Solution 10 mg. per ml. 2% cream Ophthalmic ointment 2 mg. per ml.	Pink (50 mg.) Pink and white (25 mg.) Red enteric-coated	— —
Promethazine	Phenergan (May & Baker)	10- and 25-mg. tablets Elixir 5 mg. in 4 ml. Solution 2.5 mg. per 100 ml. 2% cream	Blue sugar-coated	—

TABLE 1.—Classification of the antihistamine preparations excluding mixtures of antihistamines and other drugs.

and the doctor's signature and address. For patients in hospital addresses are unnecessary and the doctor's initials instead of his signature are acceptable. Only private prescriptions can carry instructions to repeat and then only twice (i.e. three dispensings in all), the prescription being retained by the pharmacist.

When prescribing any antihistamine drug for the first time in a patient who is up and about, it is wise to warn him against driving a car in case drowsiness and slight disorientation should interfere with his alertness or judgment. The effect of a single dose of most antihistamines wears off in about six hours, and so three doses a day are needed for continuous effect. Promethazine and chlorcyclizine have a more prolonged action. Tolerance to antihistamines develops when they are used over long periods. Because of variation in individual susceptibility, particularly to the side-effects, it is wise to avoid barbiturates, aspirin and alcohol until the reaction to antihistamines is seen. Many antihistamine tablets are sugar-coated and attractively coloured. They should be kept well out of the reach of children.

The following is a brief account of the clinical conditions in which antihistamine drugs are of value, and the preparations recommended.

ANTIHISTAMINES IN ALLERGIC CONDITIONS

Urticaria.—Most cases of acute urticaria respond to antihistamines and even though the skin lesions persist, the itching is greatly relieved. It may be necessary to push the dose until side-effects appear. Chronic urticaria does not respond so well. Antazoline, 100 mg. subcutaneously, if given early, will often abort an attack of acute urticaria or a generalized reaction to bee stings. In atopic dermatitis, pruritus is generally relieved. Creams applied locally are helpful because of their local anæsthetic action but they should not be applied for more than a week or so, lest they cause local sensitization eczematous reactions. When allergic conjunctivitis complicates skin lesions, relief can be obtained by antihistamine eye drops—antazoline, 0.5 g. per 100 ml.—or an eye ointment.

Drug reactions.—In cases of known sensitivity to antibiotics and liver preparations a tablet of an antihistamine drug before each dose will often allow valuable therapy to be continued

Muscle cramps.—These are often relieved by diphenhydramine, which is especially valuable during pregnancy when quinine is contraindicated.

Asthma.—Although antihistamines will reduce bronchospasm induced by histamine in guinea-pigs, they are of little value in human asthma, for bronchospasm in the human subject is not a simple histamine effect. Antihistamines are inferior in effectiveness to other remedies for asthma. Promethazine, however, has proved useful in asthma because of its sedative effects. By its use the patient can be given restful sleep without the respiratory depression which is a dangerous side-effect of many other sedatives. In this respect it has similar indications to paraldehyde, but it is less objectionable.

Hay Fever.—The oral use of long-acting antihistamines such as promethazine, particularly in a mild case, will often greatly relieve the symptoms of hay fever. Topical application is much less effective. Chlorcyclizine is less likely to cause side-effects. Perennial vasomotor rhinitis is much less amenable. In any individual case it is for the patient to decide whether or not the use of an antihistaminic drug and its possible side-effects are preferable to hay fever.

Serum sickness.—The generalized urticaria of serum sickness and similar rashes from drugs will often respond to full doses of long-acting antihistamines. Similar reactions to penicillin and other antibiotics are often greatly relieved by antihistamine drugs. The giving of antihistamines with antibiotics, however, has little to recommend it for, as a rule, the reaction occurs long after the effect of the antihistamine drug has gone. Even so, in cases in which one knows that a quick reaction to penicillin may be expected it is claimed that this can be prevented by mixing 10 mg. of chlorpheniramine with penicillin in the same syringe.

ANTIHISTAMINES IN NON-ALLERGIC CONDITIONS

Motion sickness.—Dimenhydrinate and promethazine chlortheophyllinate ('avomine') have greater reputations for the prevention of sea sickness. The beneficial effect does not seem to be due to simple sedation. The drug should be given at least thirty minutes before subjection to the unusual motion.

Vomiting.—The drugs recommended for motion sickness are effective in suppressing vomiting in pregnancy and following operations and x-radiation.

ANTIHISTAMINE COMBINATIONS

Two or more antihistamine drugs may be combined in a tablet to achieve potentiation of action. An example is 'dibistin' (Ciba), which consists of antazoline, 50 mg., and tripelennamine, 25 mg., in a pale yellow sugar-coated tablet. Another drug, e.g. hyoscine, may be combined with an antihistamine as in 'benacine' (Parke Davis) in which diphenhydramine, 25 mg., is combined with hyoscine, 1/200 grain (0.3 mg.), in a capsule. It is useful in motion sickness. A sedative antihistamine such as diphenhydramine may be given with a stimulating one such as phenindamine.

WHICH PREPARATION SHOULD THE PRACTITIONER USE?

The doctor who has become familiar with the actions and side-effects of one preparation is advised to stick to it. As all the preparations are effective in some patients it would be wrong to recommend one to the exclusion of all others.

The practitioner is advised to become familiar with one preparation in each of the three groups. This does not mean that antihistaminic treatment has failed when no response is obtained when one might be expected. Another drug should be given a trial. The following considerations may help in the choice. Antazoline is the least toxic, but at the same time the

weakest. Diphenhydramine is undoubtedly the most sedative, and so should be avoided for day-time use, but is very useful at night, and in cases in which a sedative effect is desired. Promethazine is the longest acting (up to twenty-four hours). Chlorcyclizine is also a long-acting antihistamine. Phenindamine is peculiar in that its chief side-effect is excitation rather than sedation. Chlorpheniramine is the newest antihistamine drug and is very rapid in action in a small dose. Oral administration of antihistamines is usual, but injection may be used to obtain a rapid effect. Although antihistamines are incorporated in many proprietary medicines, it is generally best to avoid blunderbuss therapy and to prescribe them alone.

OTHER USES OF ANTIHISTAMINES

Blood transfusion.—It is claimed that the addition of diphenhydramine (25 mg. of 'benadryl parenteral'), or chlorpheniramine (10 mg.), to a bottle of blood will abolish the allergic transfusion reactions which sometimes complicate this procedure.

Anaphylaxis.—In a severe anaphylactic reaction, in addition to adrenaline and hydrocortisone, diphenhydramine can also be given. At the Mayo Clinic a 10-ml. ampoule of diphenhydramine is provided in the emergency set to combat anaphylaxis.

Worms.—It has been claimed that 97 out of 100 adults and children infected with threadworms (*Enterobius vermicularis*) were freed of infection by a single oral dose of 125 mg. of promethazine administered at bedtime. (This drug is allied to phenothiazine, previously used for the treatment of threadworms, but found to be very toxic.) No morning drowsiness resulted. If confirmed this would appear to be a simple, effective, one-dose, non-toxic treatment for threadworms.

SIDE-EFFECTS

Antihistamines may on occasion cause side-effects which must be distinguished from the symptoms of the disease being treated. In addition to the common sedative side-effect already mentioned (most marked with diphenhydramine and absent with phenindamine) there are many less frequently encountered side-effects. Some patients experience nausea and anorexia and to avoid these the drug should not be given on an empty stomach. Prolonged treatment has caused agranulocytosis and hæmolytic anæmia. Tripelennamine ('pyribenzamine') may cause difficulty in micturition from spasm of the bladder sphincter. Photosensitive dermatitis following local application has been described.

CONDITIONS FOR WHICH ANTIHISTAMINES ARE USELESS

These include the collagen diseases (e.g. lupus erythematosus, polyarteritis nodosa, dermatomyositis), the common cold and tuberculosis. The futility of claims of effectiveness of antihistamines in many other conditions can easily be seen by any practitioner who is well versed in the natural history of the disease in question.

BRONCHODILATORS

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Bronchodilator drugs increase the diameter of small bronchi and bronchioles by reducing œdema or by relaxing smooth muscle. They may be divided into physiological bronchodilators which exert their effect in normal as well as in pathological conditions, and conditional bronchodilators which are effective only in special circumstances (table 1).

Physiological Bronchodilators
(1) Sympathomimetic drugs—Adrenaline. Ephedrine. Methoxyphenamine. Isoprenaline. Amphetamine sulphate.
(2) Xanthine derivatives—Aminophylline. Caffeine.
(3) Belladonna group—Atropine. Stramonium.
(4) Nitrites—Amyl nitrite. Sodium nitrite.
(5) Miscellaneous—Pethidine. Khellin.
Conditional Bronchodilators
(1) Antihistamine drugs.
(2) Corticotrophin, various corticosteroids and their derivatives.

Table 1.—Classification of bronchodilators.

These drugs are mainly used in the symptomatic treatment of asthma, and to a smaller extent in bronchitis and emphysema. Their relative values vary considerably.

SYMPATHOMIMETIC DRUGS

These include the most effective agents in practice. They exert their effects partly by relaxing the tone of bronchial smooth muscle and partly by contraction of small blood vessels in the bronchial submucosa, with consequent reduction of œdema.

Adrenaline hydrochloride, 1:1000, in doses of 5 to 15 minims (0.3 to 1 ml.) subcutaneously, is usually effective in asthmatic attacks of moderate severity, improvement starting within five minutes of injection. In more severe attacks or in status asthmaticus, when the initial dose has produced little effect, further increments at the rate of 1 to 2 minims (0.06 to 0.12 ml.) each minute up to a total of 50 to 70 minims (3.5 to 4.5 ml.) may be given unless symptoms of hyperadrenalinism (tremor, palpitations, anxiety) develop. Although much of the injected adrenaline is destroyed locally and vasoconstriction delays absorption, it is dangerous to continue its administration beyond the stated dose, because adrenaline shock may supervene. In this condition the blood pressure falls, the patient is collapsed and may lose consciousness. Other risks associated with the exhibition of adrenaline are cerebral hæmorrhage, transient hemiplegia and ventricular tachycardia including fatal fibrillation: such misfortunes are only likely to follow grossly

excessive dosage or technical errors in administration. It is therefore important to give precise instructions to patients who are trusted to give their own injections: in particular the gentle withdrawal of the plunger of the syringe after the needle has penetrated the subcutaneous tissues, but before adrenaline is injected, helps to minimize the risk of accidental intravascular injection.

Adrenaline may also be given subcutaneously in an emulsion of peanut oil, which retards and prolongs its effect and is thus useful at night or in patients with low-grade chronic asthma. It is also given as an aerosol in strengths of 1:100 or 1:200.

Refractoriness to adrenaline may occur in severe status asthmaticus; normal response is often restored after aminophylline or cortisone has brought about temporary improvement. Those who have employed subcutaneous adrenaline as a means of symptomatic relief of asthma for years observe no tendency for refractoriness to develop or for the drug to become less effective unless there is infection of the bronchial tract, when its value is temporarily reduced. There is no tendency for the blood pressure to become permanently raised even after daily administration of the drug for many years.

Ephedrine has a less pronounced bronchodilator effect than adrenaline but its action persists for a longer time. Repeated doses show a rapidly diminishing bronchodilator response but continue to cause cerebral stimulation which, in cases of extreme overdosage, may lead to generalized convulsions. The usual effect of cerebral stimulation is to cause a state of excitability and mental tension which some people find so distressing, even after normal pharmacological dosage, that they are unable to tolerate it. It has the advantage, however, that the respiratory centre shares in the stimulating action. Cardiovascular side-effects are also prominent. Children, oddly enough, seem relatively far more tolerant of ephedrine than adults and are rarely kept awake by a prophylactic dose given at bedtime.

It is best administered orally as a prophylactic or at the beginning of mild attacks in doses of ½ grain (30 mg.) for adults or children above the age of 10, and ⅛ to ¼ grain (8 to 16 mg.) in younger children. It may also be given in the form of a linctus at night: the following prescription is suitable for a child of six years:—

Camphorated tincture of opium	10 minims (0.6 ml.)
Oxymel of squill	15 minims (1 ml.)
Potassium iodide	1½ grains (100 mg.)
Ephedrine	¼ grain (16 mg.)
Chloroform water	to 1 fluid ounce (28.5 ml.)

Patients suffering from emphysema may benefit from regular treatment with ½ to 1 grain (30 to 60 mg.) thrice daily.

Methoxyphenamine (*'orthoxine'*) is a relatively new analogue of ephedrine and is useful in patients who are unable to tolerate ephedrine because of its side-effects. It is prescribed in the form of tablets in doses of 50 to 100 mg.

More potent than ephedrine in its bronchodilator action, its cerebral and cardiovascular effects are considerably reduced. As with ephedrine there is no advantage in giving larger doses than 100 mg. three times daily.

Isoprenaline also has an adrenaline-like action with reduced toxic effects. It differs from ephedrine in causing a fall of systemic blood pressure due to vasodilatation but many patients find that they suffer from palpitations after oral administration. It can be absorbed sublingually in the form of 20-mg. tablets but it is most effective and most free from side-effects when administered in the form of an aerosol (in 1 per cent. solution), usually delivered by a hand pump. Mild attacks can be aborted in this way by inhalation of five or six breaths: more severe attacks by continuous inhalation of the aerosol for fifteen to thirty minutes, delivered by means of pressure from an oxygen cylinder or an electric motor.

Amphetamine sulphate is prescribed for its stimulating action on the central nervous system. It has, however, a mild bronchodilator action, and beneficial effects on respiration have been noticed incidentally when it has been given for the treatment of depression in emphysematous subjects.

It is important to remember that the only preparations in the sympathomimetic group effective in status asthmaticus are adrenaline injections and prolonged inhalations of isoprenaline. The action of all these drugs is diminished by bronchial infection.

XANTHINE DERIVATIVES

Theophylline and caffeine are both employed for their bronchodilator effect. They also exert a central action, which includes stimulation of the respiratory centre and a direct action on the heart muscle. Because of the last, these substances are particularly valuable in cases of cardiac asthma.

Theophylline is usually prescribed as ***aminophylline*** (theophylline with ethylenediamine) and is most effective when given intravenously in doses of 0.25 to 0.5 g. Because of its direct action on the heart, which may cause palpitations and, very rarely, sudden death if improperly administered, it is important to give it very slowly. Dramatic relief of spasm in severe asthma may be brought about in patients who have failed to respond to adrenaline. In status asthmaticus the dose may be repeated four- to six-hourly, up to a total dose of 2.5 g. in twenty-four hours. It may also be given in a saline glucose drip, particularly if there is evidence that the patient is dehydrated. It may be alternated with subcutaneous injections of adrenaline, since each drug seems to enhance the effect of the other. Preparations for intramuscular injection can also be given but are often painful and far less effective than when given intravenously. Aminophylline can also be given orally in 3-mg. tablets but many patients are unable to tolerate it because of the irritating effect on the gastric mucosa which may cause abdominal pain. This can be overcome by combining it with a demulcent such as aluminium hydroxide gel or with choline (choline theophyllinate). Oral administration,

however, is only of value in treating or preventing minor attacks. Rectal suppositories containing 250 to 500 mg. of aminophylline are sometimes useful when taken at night to prevent early morning wheezing.

Caffeine is somewhat less effective as a bronchodilator but has a more pronounced action on the central nervous system. It is, however, particularly valuable in cases with tenacious sputum if prescribed with iodides, as in caffeine iodide elixir N.F.:—

Caffeine and sodium iodide	5 grains (0.3 g.)
Sodium iodide	5 grains (0.3 g.)
Liquid extract of liquorice	5 minims (0.3 ml.)
Chloroform	⅛ minim (0.008 ml.)
Decoction prepared from a sufficient quantity of prepared coffee and water	to 60 minims (4 ml.)

60 minims (4 ml.) four times daily.

BELLADONNA GROUP

Although these drugs (atropine and hyoscyamine) act by inhibiting the effect of post-ganglionic cholinergic nerve fibres and hence relax smooth muscle and reduce the secretion of bronchial mucus, their action in asthma is disappointing. It has been suggested that the bronchial secretions, though reduced in quantity, are rendered more tenacious and that the difficulty of expectoration is therefore increased. The dryness of the mouth and the effect on accommodation are unpleasant if large doses are used. Their use in asthma is practically limited to the prescription of tincture of stramonium which is of some value in combination with potassium iodide in asthma secondary to bronchial infection. The *National Formulary* preparation is satisfactory:—

Potassium iodide	3 grains (0.3 g.)
Tincture of stramonium	20 minims (1.3 ml.)
Chloroform water	to ½ fluid ounce (15 ml.)

Stramonium leaves are the active ingredients of some proprietary asthma powders, intended for use by burning and inhalation of the smoke.

NITRITES, PETHIDINE AND KHELLIN

Nitrites.—These relax bronchial muscle. They are of no practical value because of the short period of effective action and because unpleasant side-effects, dependent upon the associated vasodilatation, are more prominent than the bronchodilator effect.

Pethidine hydrochloride has a moderate effect in relaxing bronchial smooth muscle in asthma. It is not sufficiently potent to use primarily as a bronchodilator drug and the tendency to addiction is a further reason for avoiding its use in a chronically recurring ailment. It is, however, of value sometimes as a sedative in severe status asthmaticus, since its depressing action on the respiratory centre is relatively slight, and because of the associated bronchodilator effect. When prescribed for this purpose it is best given in doses of 50 mg. by intramuscular injection together with adrenaline hydrochloride

(1:1000), 10 minims (0.6 ml.), and nikethamide, 2 ml., in the same syringe.

Khellin is a smooth-muscle relaxant which may be effective in controlling or preventing mild attacks of asthma. It has no advantage, however, over the cheaper and more readily available drugs of the sympathomimetic or xanthine group. In many people it causes nausea, epigastric discomfort and diarrhœa. It is prescribed in keratin-coated tablets (20 to 50 mg.) or in the form of rectal suppositories.

ANTIHISTAMINES

Histamine is undoubtedly liberated as a result of antigen-antibody reactions of the immediate allergic (atopic) type. Moreover histamine inhaled as an aerosol or by injection will cause asthma. The relative failure of antihistamines as bronchodilators in asthma therefore has been one of the major disappointments of modern pharmacology. Although they are capable of relieving artificially produced histamine-induced asthma in animals or man, they are of little value in the treatment of naturally occurring asthma. Promethazine in particular is poorly tolerated by many on account of its prolonged sedative action. The associated sedative effect of diphenhydramine and promethazine, however, makes them suitable preparations in nervous children with nocturnal bronchospasm of moderate severity. Diphenhydramine may be prescribed as an elixir which is suitable for children between 5 and 10 years of age:—

Diphenhydramine	0.08 g.
Chloroform	0.1 ml.
Lemon flavouring	0.12 ml.
Liquid extract of liquorice	0.03 ml.
Solution of Bordeaux B (B.P.C. 1949)	0.08 ml.
Solution of burnt sugar B.P.C.	0.1 ml.
Syrup	to 28.5 ml.

4 ml. at bedtime.

Promethazine may also be given as an elixir, in doses of 5 mg. in 4 ml., with suitable colouring and flavouring agents.

CORTICOTROPHIN AND CORTICOSTEROID PREPARATIONS

These preparations certainly have no direct bronchodilator action, but they undoubtedly exert a beneficial effect over a short period of time in most cases of asthma, increasing the vital capacity and reducing bronchiolar resistance, and for this reason they merit inclusion in this article. They are probably of most value when given in short courses of one to two weeks during attacks of status asthmaticus or in asthma which has failed to respond to the usual symptomatic remedies and which may, if unchecked, pass into status asthmaticus. The unpleasant side-effects, chiefly the development of some or all of the manifestations of Cushing's syndrome, and, in the case of the corticosteroids, the risk of suppressing the patient's own adrenal glands makes their use as a long-term form of therapy a matter of serious consideration. Except as a lifesaving measure they should not be used even

for short periods in patients with recently active tuberculosis, peptic ulcer, nephritis or psychotic tendencies. They are less likely to be effective when there is gross bronchial infection, and in these circumstances they should be given with antibiotics.

The two new analogues of cortisone and hydrocortisone, prednisone and prednisolone, have a diminished tendency to cause salt retention and hypertension and for this reason have some advantages over the naturally occurring steroids.

In *status asthmaticus* the following courses of treatment are usually effective:—

Corticotrophin given in the form of long-acting preparations by intramuscular injection:—

40 mg. twice daily for two days.
30 mg. twice daily for two days.
20 mg. twice daily for four to seven days.
20 mg. daily for two days and 10 mg. for one day.

Cortisone: 300 mg. in divided doses orally on the first day, followed by 250 mg., 200 mg., 150 mg. on successive days. On the fifth day 100 mg. is given in four doses of 25 mg. and reduced to 50, and 25 mg. after seven to ten days.

Hydrocortisone is given in comparable courses, the dosage being approximately two-thirds that of cortisone, whilst prednisone and prednisolone are prescribed in doses five times smaller. For the control of less severe attacks a smaller maximum dose is required, say, 40 mg. of long-acting corticotrophin gel, 100 mg. of cortisone, 50 mg. of hydrocortisone and 20 mg. of prednisone or prednisolone, the whole course of treatment occupying seven to ten days.

SUMMARY

From the wide choice of bronchodilator drugs suitable selection must be made according to circumstances. For the prevention of nocturnal attacks, oral ephedrine, aminophylline or a combination of these are most suitable. Methoxyphenamine may be substituted for ephedrine in those who are intolerant of the effects of the latter on the central nervous system or heart. To abort minor attacks, these drugs, or isoprenaline in an atomizer, are usually effective; if the attacks are more severe small doses of adrenaline may be given subcutaneously. When spasm is associated with bronchial infection a mixture containing stramonium and potassium iodide or elixir of caffeine iodide is preferable. If the infection is heavy, antibiotics must be employed.

In severe attacks, or in status asthmaticus, repeated injections of subcutaneous adrenaline, or of aminophylline intravenously, will often give relief, but in those patients who have failed to respond to these measures corticotrophin or cortisone will usually be effective unless emphysema is severe or there is heavy bronchial infection.

DIURETICS

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Diuretics may be divided into three main types according to the mechanism by which they increase the output of urine.

CLASSIFICATION

First are those procedures and drugs which improve the blood supply to the kidneys and thereby increase the amount of water and solutes filtered by the glomeruli. Thus, the oliguria associated with trauma and surgical shock is corrected by transfusions of blood or plasma; that caused by dehydration and sodium depletion by infusions of saline; and that due to heart failure by rest and the improvement in cardiac function that follows digitalization. The xanthine group of drugs exert a diuretic action by increasing renal blood flow but their effect is transient.

Second are those substances which induce an osmotic diuresis by impeding the reabsorption of water in the renal tubules. This is the cause of the polyuria in diabetes mellitus—the large amount of sugar, filtered by the glomeruli because of the high blood level, preventing the reabsorption of tubular water. Urea is the most commonly used example of this type of diuretic.

Third, and most important, are substances that prevent the reabsorption in the renal tubules of various anions and so enhance the excretion of sodium. The organic mercurial diuretics, ammonium chloride and acetazolamide ('diamox') are examples of this group, and the mercurial diuretics are incomparably the most effective.

In many diseases diuretics provide only symptomatic treatment and whenever possible the underlying disease process itself must be treated. Thus, although mercurial diuretics are useful in controlling œdema due to thyrotoxic heart disease, the primary disorder is the hyperthyroidism, and ultimately this is what must be put right. Similarly in mitral stenosis diuretics may be most helpful in controlling cardiac failure, but whenever possible the valvular stenosis must be relieved surgically and failing this the action of the heart maintained at its maximum with digitalis. To give a mercurial diuretic to a patient in congestive cardiac failure without the benefits of bed rest and digitalis is a contradiction of therapeutic principles.

INDICATIONS

Diuretics are given whenever salt and water are retained in the body as shown by the development of œdema or a rapid gain in weight. The main conditions responsible for this state of affairs are congestive heart failure due to any cause, pulmonary œdema and congestion, nephrosis, and ascites due

to hepatic cirrhosis. In general the greater the œdema, the greater is the diuresis, but a gratifying increase in urine output may occur when the water and salt retention is not sufficient to cause pitting œdema. Thus nausea and anorexia due to painful congestion of the liver, and engorgement of the neck veins may be relieved, and attacks of suffocating paroxysmal nocturnal dyspnœa ('cardiac asthma') stopped by giving a diuretic *in conjunction with other appropriate treatment*.

Limitation of salt intake.—In addition to diuretics, patients with severe congestive failure may have to restrict their intake of sodium and, with intractable failure, to eat a salt-free diet. In less severe cases and in ambulant patients a salt-poor diet without any diuretic may keep the patient œdema free but many find such a diet irksome and unpalatable. Their enjoyment of life is much enhanced if they are allowed a normal diet, omitting only obviously salty dishes and excessive salt from the cellar, and are given diuretics even if this entails an injection of mersalyl once or twice weekly.

MERCURIAL DIURETICS

Route of administration.—As the most effective diuretic, mersalyl by intramuscular injection still retains pride of place against all newcomers. It acts by interfering with the tubular reabsorption of chloride, 20 per cent. of the filtered load being excreted in combination with sodium and a lesser amount of potassium. It is relatively non-toxic: one patient, for instance, has received 627 injections in twelve years without any ill-effects. Although some 30 deaths, attributable to the toxic action of the mercury on the myocardium, have been reported following injections of mersalyl, in every instance the injection has been made intravenously. Since there is no convincing evidence that mersalyl is more effective intravenously than intramuscularly, it should *always be given intramuscularly*—preferably into the lateral aspect of the thigh or the upper outer quadrant of the buttock. Truly intramuscular injections are seldom painful but some patients tolerate one preparation better than another, and if discomfort is experienced after repeated injections of mersalyl, a change should be made to 'neptal' or 'salyrgan'.

To avoid the inconvenience of intramuscular injections a new mercurial diuretic, mercaptomerin sodium ('thiomerin'), has been introduced which can be given subcutaneously, if necessary by the patient himself. Its effect is equivalent to that of mersalyl but unfortunately in about 20 per cent. of patients there is unacceptable pain and swelling at the site of injection.

Mersalyl by mouth or by suppository is rarely satisfactory and soon gives rise to diarrhœa or proctitis. The most promising oral mercurial diuretic is chlormerodrin ('mercloran'). This is of value in keeping ambulant patients, who have recovered from congestive failure, œdema free. The smallest effective dose should be used: one tablet thrice daily on alternate days is usually sufficient but even in this dosage diarrhœa may occur.

Dosage, frequency and duration of treatments.—An initial trial dose of 0.5 ml. of mersalyl should be given intramuscularly. If there are no untoward

reactions (rigor, nausea, vomiting, pain at the injection site, or rash), the full dose of 2 ml. is given early on the morning of the next day so that the diuresis does not disturb the patient's sleep. Most of the mercury is excreted

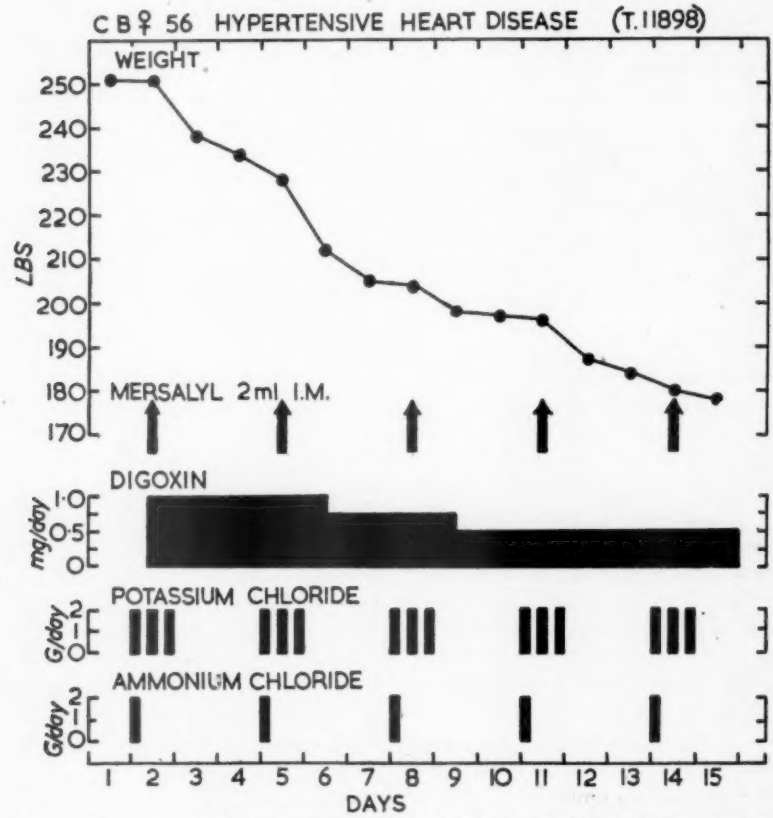

FIG. 1.—The response of a woman, aged 56, with hypertensive heart disease who lost 72 lb. (32.5 kg.) of œdema fluid (equivalent to 33 litres or 7 gallons) in a fortnight. Unusually large amounts of adjuvant treatment with potassium and ammonium chloride were given because she had been in congestive failure for many months before treatment was started. The biggest single response to mersalyl (16 lb. [7.3 kg.] equivalent to 7 litres of fluid) was after the second injection. Note the gradual diminution in response as she reached her 'dry weight'.

within twenty-four hours and elimination is virtually complete in three days. Thus, except in the most urgent cases, the injections should be given not more often than every third or fourth day. Later, with improvement they can be reduced to once weekly.

This treatment should be continued until the patient is œdema free or ceases to have a diuretic response, as determined by measurement of the

difference between fluid intake or urine output or, more simply and practically, by recording the daily weight (see fig. 1). Failure to respond to mersalyl in the face of persisting œdema is usually due to excessive loss of chloride without a parallel loss of sodium (hypochloræmic alkalosis), sodium chloride depletion (low-salt syndrome), potassium depletion, or a grossly impaired renal circulation. The biochemical causes of mercurial refractoriness can largely be prevented by prescribing, simultaneously with the mersalyl, the adjuvant therapy outlined below. When low renal blood flow is the cause, a response may be initiated by injecting intravenously 0.5 g. of aminophylline two hours after the mersalyl has been given.

Adjuvant therapy.—Ammonium chloride synergises the effect of mersalyl by providing chloride ions, prevents the development of mercurial refractoriness, and has a diuretic action in its own right. Potassium chloride also provides chloride ions, and the potassium helps to restore the depleted body stores and prevents the development of hypokalæmia which increases the liability to digitalis intoxication. Thus, two hours before receiving mersalyl the patient should take two enteric-coated capsules, each containing 0.5 g. of ammonium chloride, and in addition two enteric-coated capsules each containing 0.5 g. of potassium chloride.

Acetazolamide also potentiates the action of mersalyl by producing an acidosis with increase of plasma chloride. Given in a single dose of 250 to 500 mg. (1 to 2 tablets) on the day of the mersalyl injection it has proved more valuable as an adjuvant than as a diuretic in its own right.

Contraindications.—Moderate albuminuria and a blood urea of less than 100 mg. per 100 ml. are not contraindications to mersalyl because they may occur in uncomplicated heart failure and indicate only a temporary impairment of renal function. A blood urea in excess of 100 mg., refractoriness despite the use of adjuvants, and reactions (faintness, rashes, diarrhœa, stomatitis) call for a halt to treatment.

OTHER DIURETICS

The amount of space given to diuretics other than the mercurials indicates their comparative value. None is satisfactory in the treatment of the type of œdema described above. Acetazolamide in a daily dose of 250 to 500 mg. has only a temporary diuretic effect which soon passes. It cannot even be relied upon to keep an ambulant cardiac patient free of œdema, but it is of value as an adjuvant to mersalyl for patients who cannot tolerate ammonium chloride. Aminophylline (0.5 g. intravenously or intramuscularly) has too transient an action to be an effective diuretic but may potentiate the action of mersalyl in a refractory case. Urea (15 g. in fruit juice thrice daily), ammonium chloride (1 g. in enteric-coated capsules thrice daily), and acetazolamide are of value in the treatment of the mild fluid retention that may occur in migraine and premenstrual tension.

LAXATIVES AND APERIENTS

By JAMES RONALD, M.D., F.R.C.P.Ed.
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Preoccupation with what Sir Thomas More termed our daily easements is universal throughout the world, and man's beliefs about the functioning of that beautiful system of geodesics that comprises the alimentary tract are as much influenced by folklore as by physiology. This interest has led to the subject being accorded a status varying between pastime and religion, and it behoves the doctor to walk warily when dealing with the obsessions and venerable traditions of his fellows. Between the pleasant—as in Harington's 'Metamorphosis of Ajax' where the reverent Fathers of the Church meditate on the divine mysteries while seated on the privy—and the unpleasant—as in the exploitation of the public by unscrupulous commercial advertising—lie the beliefs and worries, true and imagined, which call for attention. Physics and metaphysics are perhaps the real answers; but life is short, and a laxative is a surprisingly good substitute.

MECHANICS OF THE BOWEL

To prescribe intelligently, it is essential to bear in mind the simpler facts of alimentary physiology. The stomach contents traverse the duodenum and small intestine in about 3½ hours, and are admitted to the cæcum in a fluid condition. Constant activity leads to complete mixing and homogeneity. Through loss of water, the bowel contents become semi-solid as they pass into the transverse, descending and pelvic colon: there is little peristalsis in the colon except for the powerful mass-movement which occurs about three times a day and is initiated by the entrance of food into the stomach. The pelvic colon is reached about twelve hours after ingestion and the contents accumulate there until defæcation. This usually occurs when the fæcal material during a period of colonic activity passes into the rectum, the distension exciting the reflex for expulsion. When defæcation occurs, the contents of the colon distal to the splenic flexure are evacuated.

There is great individual variation in bowel function; experiments with ingested seeds and glass beads suggest that about a week may be taken in clearing material from a given meal. These points are of practical importance since after a laxative has been used the colon is empty, and no subsequent evacuation should be expected until the colon has gradually refilled.

THE USE OF LAXATIVES AND APERIENTS

Since ritual purgation has diminished, the use of laxatives is to a large extent dictated by the patient's comfort. When an upset of bowel habit

occurs and the patient seeks advice, it is the doctor's first duty to ensure that there is no local or systemic disease responsible. A clear history is important and conditions such as myxœdema or diabetes mellitus may be easily recognized clinically, but a full investigation should be carried out if necessary. When the condition is functional and not organic in origin, simple measures may be adequate. The most common cause of sluggish bowel action is failure of sufficient food residue to reach the colon, and improvement can be expected following increase of water and cellulose intake. When there is spasm or inactivity of the colon, a sedative may be the best aperient, either alone or in conjunction with belladonna. Through neglect in the hurly-burly of modern life, the rectum may have become insensitive and hence may not answer the call to defæcation. In such circumstances purgation is useless; the bowel should be cleared by enema and re-educative measures instituted. Patience is required to ascertain the relevant points and to discuss their significance and treatment, but the time spent is well repaid by the relief granted to doctor and patient. Intelligent cooperation can move more than mountains.

The word 'constipation' is probably best avoided since everyone understands it without knowing what it means; presumably a person is constipated if he suffers a delay in defæcation sufficient to cause discomfort or worry to himself or his medical adviser. There is no absolute value in bowel habit.

If the desired effect is not produced by the measures adopted, recourse must be made to the use of laxatives and aperients. The aim should be to produce a soft motion without griping or πομφολυγοπαφλασματα. Whilst there are various objections to different laxatives, it should not be forgotten that any of them can be given in safety to selected patients provided suitable doses are employed. It is therefore more sensible to become fully familiar with the use and capabilities of two or three drugs alone or in combination than to use a large number of different ones.

The drugs employed fall roughly into two groups: those affecting the bulk or consistency of the stool, and those irritating the alimentary tract.

BULK AND CONSISTENCY VARIATION

Speedy emptying of the bowel may be induced by a *glycerin suppository* (suppositories of glycerin B.P.; medium or large size) or a soap and water *enema*. A rapid action, often within an hour, can be obtained by the use of *salines*, which are best taken dilute before breakfast. They act by hastening the contents of the small bowel into the large intestine and produce a loose and sometimes watery motion. Suitable preparations are sodium or magnesium sulphate, ½ to 1 ounce (15 to 30 g.), and the more palatable Seidlitz powder (compound effervescent powder B.P.).

The bulk-increasing agents are best given in divided doses since there is considerable variation in individual requirements. Of these, *liquid paraffin*,

¼ to 1 fluid ounce (7 to 30 ml.), can be used as an occasional laxative but is unsuitable for prolonged use because of the risks of anal leakage, indigestion, and the production of vitamin-absorption defects. The best material is *agar-agar* (60 grains [4 g.]) used in shredded form or as a powder. It is a non-irritant, non-absorbable, carbohydrate gelose. Numerous emulsions containing paraffin and agar are available but unfortunately the majority also contain phenolphthalein. Agar is best prescribed alone. The increase in fæcal volume brought about by the addition of a few grammes of cellulose to the diet is considerable, since 75 per cent. of the total weight of fæces consists of water.

IRRITANTS

A large number of substances act directly on the gut, some, such as the organic acids in figs and prunes, gently, others violently. *Castor oil* (⅛ to ½ fluid ounce [4 to 15 ml.]), though somewhat out of favour among children, is effective and produces a soft stool in three to six hours.

The anthracene group of laxatives is deservedly popular. Habituation is slow to develop, and the active principles affect the large intestine. Griping, however, is sometimes produced, although it can be minimized by the addition of an antispasmodic. They are moderately quick in action, and can be taken at night in order to produce a motion in the morning. *Cascara* is useful either in liquid form, elixir of cascara sagrada B.P. (30 to 60 minims [2 to 4 ml.]), or as a tablet in combination with rhubarb and nux vomica (compound tablets of cascara sagrada B.P.C.: dose 1 to 2 tablets). *Rhubarb* should be avoided unless combined with other drugs, since the tannin produced tends to constipate. Slightly more powerful, though somewhat longer in taking effect, is *aloes* (pill of aloes B.P. 1948: 4 to 8 grains [0.25 to 0.5 g.]) which should be used with caution in pregnancy since it may stimulate the uterus. *Senna* has long been employed both alone as an infusion (4 to 12 pods) and in many combinations. Its disadvantages were overcome with the isolation of the glycosides and these provide an effective agent free from side-effects ('senokot').

Phenolphthalein, 1 to 5 grains (0.06 to 0.3 g.), has a general effect resembling that of the anthracene group, but its action is cumulative. Although it has the advantage of being almost tasteless, it is best avoided in children as it may have toxic effects.

Mercury (mercurous chloride B.P.: 1 to 5 grains [0.06 to 0.3 g.]) is most effective in repeated small doses. It is not without danger since retained traces may be absorbed or produce bowel irritation and diarrhœa; the administration of a saline the following morning will avoid this. The hydragogue cathartics act powerfully by virtue of their highly irritant glycosides. They are quickly cleared from the bowel, but should be rarely required. They include *jalap* (compound powder of jalap B.P.C. 1949: 10 to 60 grains [0.6 to 4 g.]) and *colocynth* (pill of colocynth and hyoscyamus

B.P. 1948: 4 to 8 grains [0.25 to 0.5 g.]). Since jalap acts on the small intestine, its prolonged effect may sometimes be of value during anti-helminthic treatment.

GENERAL ASPECTS

In the use of laxatives, as in so many other medical matters, faith plays a part. If a patient has been in the habit of taking a certain laxative regularly, and has found it satisfactory, there is nothing to be gained by changing it. Indeed such a procedure, even though backed by the might of science, is much more likely to upset than to help him. Argument is useless, and controversy engenders more heat than light. Discretion should be shown in the prescribing of proprietary drugs. In spite of theoretical considerations, there is no doubt that some proprietary preparations are more successful than the apparently identical official remedy. If this difference is manifest in a particular instance, then the welfare of the patient comes first. Common sense will usually aid in resolving difficulties, but discussion with more experienced colleagues and reference to official publications such as the *National Formulary* may be wise, since the doctor must be able to justify such action as he takes.

For practical purposes the use of laxatives may be regarded as occasional, temporary or permanent. Occasional usage is indicated when a person, perhaps following a dietetic or alcoholic indiscretion, feels that a bowel action might improve his condition. A brisk saline purge or dose of cascara will usually prove adequate. Temporary requirements, as for instance when a patient is confined to bed through illness, accident or operation, may be met by senna or aloes; in view of physiological considerations, the drug should not be required more often than twice a week. When laxatives are needed permanently through age, lack of intelligence or cooperation, chronic invalidism, or failure to respond to simple measures, the bulk-increasing preparations are of most value, and the addition of an anthracene aperient occasionally may also be helpful. Habituation must be guarded against, and treatment varied as circumstances change. In all circumstances severe purging should be avoided, and since the intensity of drug action depends upon the dosage, the amount given should be adjusted to produce a single soft but not watery motion, preferably in the morning.

SPECIAL INDICATIONS

It has already been remarked that the best results are to be obtained by knowing a few drugs intimately. It may be desirable in some instances, however, to be familiar with alternative measures. As John Bunyan said, 'It would be tedious to tell you of all; we will therefore only mention a passage or two more'.

When aperients are required during *pregnancy*, the more powerful should be avoided for obvious reasons. Paraffin-agar emulsions are safe and the dose

can be graduated to meet the occasional requirement. Most preparations contain phenolphthalein, but 'petrolagar plain' is free of this disadvantage, and contains 66 per cent. liquid paraffin and 20 per cent. agar jelly.

In *children*, where palatability is an important point, syrup of figs (compound syrup of figs B.P.C., 30 to 120 minims [2 to 8 ml.]) containing rhubarb, senna and cascara, or syrup of senna B.P. (15 to 30 minims [1 to 2 ml.]) may be useful. An unsweetened preparation suitable for an infant is cream of magnesia (mixture of magnesium hydroxide B.P., 30 minims [2 ml.]). Mercurial compounds such as grey powder should never be given in view of their toxicity and the risk of severe fluid loss.

The *incontinent elderly patient* may be helped by an enema of 4 fluid ounces (120 ml.) of a 5 per cent. solution of calcium chloride. It is easily administered, gives rise to no distress, yields an immediate result, and avoids soiled linen. In elderly or cardiac cases, in which enemas are not tolerated and minimum disturbance is advisable, a contact laxative which increases colonic activity without causing local irritation may be used as a suppository: e.g. 'dulcolax', 10 mg. When fæces have become hardened, and in cases in which there is pain from anal fissure, a softening effect can be obtained by means of a synthetic anionic 'wetting' agent, dioctyl sodium sulphosuccinate ('dioctyl-medo' contains a 0.25 per cent. solution in syrup of orange). The dose is varied as necessary.

TAILPIECE

The successful use of laxatives is simple provided that too much is not attempted or expected, and that patient and doctor are *simpático*. Bowel obsessions, however, bring with them problems sometimes insoluble, and for these one can but commend to the physician Paish's epigram,

> 'Faced with the Gordian knot
> Untie it if you can, cut it if you dare.
> But if you can do neither, don't despair.
> The rope will rot'.

OUR HERITAGE AND OUR FUTURE*

By IAN D. GRANT, M.B., Ch.B.
Glasgow

'Honour a physician with the honour due unto him, for the uses which ye may have of him: for the Lord hath created him'. *Ecclesiasticus* xxxviii, 1.

At the turn of the present century the general practitioner had become the Cinderella of the profession. It was not until Mackenzie startled the world with his work on the irregularities of the pulse and revolutionized the whole treatment of heart disease that the giants of Harley Street realized that worth-while work and research could be successfully undertaken by one engaged in general practice. All of us are familiar with the legend that has grown round Mackenzie, but many of us may not be so cognizant of the difficulties which he encountered and the prejudices he overcame. We may therefore find it profitable to reflect for a little on the life and work of one who so well merited the title of 'the beloved physician'.

MACKENZIE'S EARLY DAYS

James Mackenzie—the son of a Scottish farmer—was born on April 12, 1853, in Scone, near the ancient abbey where, from remotest antiquity, the Kings and Queens of Scotland were crowned. There was little in his early life to foreshadow the greatness to which he attained or the impact he would make on the medical thought of his own and future generations. He had no overwhelming desire even to become a doctor—indeed his first love was to engage in pharmacy, and it was not until he was 21 years of age that he went to Edinburgh to begin the study of medicine. His undergraduate career—like his schooldays—was not especially distinguished although in his final year he surprised and delighted both himself and his friends by gaining three medals. All through his University career he protested that he could never understand why teachers should set so great a store on the exercise of memory and the ability to reproduce other people's phrases, teaching and opinions, and so small a store on the exercise of reason, personal observation and deduction. When he himself was acclaimed as a great teacher he spoke thus to a session of the Royal College of Physicians:—

'The outcome of the teaching of today is to hail the student with superior powers of memorizing as the brilliant student and the one with the great future. In the absence of any knowledge acquired from his own observations, he is forced to teach that which he was himself taught, and as he cannot distinguish between truth and superstition he hands both on to his students'.

*The third James Mackenzie Lecture, delivered before the College of General Practitioners on November 17, 1956.

Dr. Grant introduced his lecture by a survey of practice from earliest times, showing that the era of the specialist did not arrive until the middle of the 19th century.

To some extent that might still be a criticism of present-day teaching.

Mackenzie graduated in 1878 and, after a term as house physician in Edinburgh Royal Infirmary, he wrote to a friend:—

'I felt a longing to devote myself to some of the branches of medicine concerned in research, but my very moderate attainments precluded me from obtaining a university post and I recognized that I was only suited for what is considered to be the lowest sphere in the medical profession'.

How little did he then realize that by his precept and example he would prove that general practice is the one place in which the early signs of disease can be studied. Through the genius of Mackenzie the stone which the builders rejected has become the head of the corner.

EARLY DAYS IN GENERAL PRACTICE

His introduction to general practice could hardly have been more arduous. He went as a locum to a colliery practice in Durham. At that time the standard of practice in the industrial area was low. The club system was the recognized method of payment for medical services where for a pittance of 6*d*. a week the doctor contracted to give medical care and all necessary drugs to the wage-earner and his family. The status of the doctor was poor. Professional ethics were deplorable, and there was keen and often unscrupulous competition, even for these ill-paid posts. The local club secretaries, almost invariably coarse and ill-educated men, exercised a nearly tyrannical control over the doctors. The whole system was degrading and depressing. Mackenzie records that the most popular remedy in the dispensary was a concoction of burnt sugar and ginger. It gripped. It had a fine colour and enjoyed a high reputation as a specific for all ailments of the digestive tract.

In 1879, this tall, kindly young Scot came as an assistant to a Dr. William Briggs in Burnley; a drab grey town where the click-clack of clogs resounded all day on the cobbles and where for the next twenty-five years Mackenzie lived and worked and played with these hard-headed but warm-hearted Northern people. For this young doctor was no ascetic. He was a good golfer, a skilled billiards player and no mean exponent of the art of boxing. Withal he was endowed with that kindly courtesy to old and young which is so necessary a prerequisite for a successful family doctor.

About 1884, Mackenzie began to formulate to himself some of the problems and difficulties he was encountering in practice and for which he felt there must be some solution. He wanted primarily to understand the causation and the mechanism of symptoms and their relationship to prognosis. And just then came to him one of those tragedies which happen to most of us at some time in our career.

A young patient died completely unexpectedly. Mackenzie was seated at the bedside of a young primipara. Her labour seemed to be progressing normally. He spoke words of comfort and encouragement to her as she moaned softly in her hour of travail. Suddenly her pulse flickered and was gone. Before his eyes she died of sudden cardiac failure. That night, as he paced the floor of his consulting room,

his confidence sadly shattered by the tragedy, he kept asking himself: 'Would she have died had I known more about heart affections?'

There and then the decision was taken. He determined to give close study to the symptomatology of heart disease with special concern for the pregnant woman. He found that it was only after disease had made considerable

No. 68, Bank Parade, Burnley, where Sir James Mackenzie practised as a general practitioner.

ravages in the body that an accurate diagnosis could be pronounced and that with early symptoms of ill health—often with no actual physical signs presenting—the only way to ascertain what a symptom betokened was to wait and watch that patient over a period of years. There was no short cut to this knowledge. The textbooks of his day gave him no satisfactory answers and so this courageous, busy practitioner evolved his own methods. At first his recording instruments were clumsy and primitive. His colleagues and friends laughed good-naturedly at him as 'the doctor with the drums and smoked paper' but he steadfastly pursued his way and gradually, without any help from the current medical literature, he came to realize that the accepted treatment of heart disease was wrong and that many people who should be leading full and active lives were condemned to invalidism and inactivity.

THE STUDY OF THE PULSE

In 1902 he published his first book, 'The Study of the Pulse'. Writing of the irregularities of the pulse he says:—

'It took me 20 years of patient observation of these irregularities in health and disease before I could prognosticate accurately'.

This volume brought him fame and recognition in Germany and America, but London was at first just faintly amused. Was he not merely a general practitioner, and what could he know that was new about the action of the heart and the treatment and prognosis of its many disorders? But although the prophet was without honour in his own country, the savants of other lands were impressed. He was invited to the United States, to Canada and to the Continent, and everywhere he was hailed as a seer and a great physician. Burnley became a place of pilgrimage for distinguished foreign scientists who wanted to see the man and to discuss with him his problems, his investigations and his deductions. The men of Harley Street, however, did not come. How could a busy general practitioner with his limited knowledge, his lack of hospital and laboratory facilities, and indeed one who still practised in the homes of the people, overthrow all the accepted teaching about heart disease?

Sir James Mackenzie.

MACKENZIE COMES TO LONDON

At the age of 54, after 25 years of patient investigation, Mackenzie decided that he would go to London and endeavour to impose his views on a doubting and reluctant profession. His first year was fraught with difficulties, and he earned only £114, but in 1908 he published his book 'Diseases of the Heart', a book which exercised an influence over current thought almost without parallel in medical history. On the cardiologists of London the impact was devastating. No longer could they ignore this North Country general practitioner. Here was a completely new exposition of the symptomatology and prognosis of disorders of the heart, and the course of each disease was illustrated with graphic records recorded at the bedside, each of which was analysed with meticulous accuracy and studied over a long period of years. The evidence in support of his conclusions was overwhelming and irrefutable. London capitulated. The new teacher was loaded with honours. He was elected a Fellow of the Royal College of Physicians. He was invited to become the head of a newly created heart department at the London Hospital where all the resources of that world-famous institution were placed unreservedly at his disposal. The wheel had indeed turned full circle and the obscure country practitioner of yesterday was hailed as the leading consultant of today.

Mackenzie gratefully and gladly accepted the honours that were conferred upon him but his colleagues had not yet accepted his fundamental principles. They honoured the polygraph more than the patient clinician, the man who

waited to see. They were shocked by some of his pronouncements, which indicated that Harley Street must adopt a new outlook as well as a new scientific instrument.

'It is not second sight which I possess but only sight. My eyes were opened because I had real need to use them. No instrument or polygraph can replace the finger, the experience and the reasoning powers of the doctor himself'.

Always he stressed the importance of the family doctor.

'The early stages of disease are as a rule insidious and are indicated mainly by subjective sensations. The patient, conscious that something is amiss with him, does not as a rule seek help from the hospital physician but rather from his family doctor. The bulk of patients in the early stage of disease are never seen by those who are systematically engaged in the investigation of these diseases'.

A distinguished American physician, having spent some time with Mackenzie, finally asked: 'What line of research would you advise me to pursue when I return home?' and the great man replied: 'I would advise you to go into general practice and stay there for ten years because it is only in general practice that a doctor can learn to foresee danger to his patient and how to take steps to prevent it'.

In due course the new principles of cardiology became established, but Mackenzie himself still insisted that research must originate in general practice. To one of his most brilliant disciples he said, sorrowfully, one day: 'If only you had had even five years in an industrial practice'.

'Common sense would say that where signs of disease are most difficult to make out, there the most experienced physician should be employed, but in no teaching hospital is this ever done. Here in the outpatient department is placed the youngest member of the staff, often lacking in experience and ignorant of the meaning of subjective signs. If there are no obvious physical signs the patient is sent away perhaps with a bottle of physic but not until physical signs are apparent does he come under the care of the senior physician. On the other hand, in the wards where his case has advanced so far as to produce physical signs—mostly easy of recognition—we have the skilled physician and all the assistance of the research laboratory'.

So wrote Mackenzie in the early years of this century, and, although his criticisms may have been severe and scathing, is there not still much truth in his plea that the trained physician should be in the outpatient department where his skill and experience may detect disease in its earliest phases?

ST. ANDREWS AND THE LATTER DAYS

Then, in 1918, the man who was hailed as the greatest cardiologist of all time decided that he would leave his consulting rooms in Harley Street and return to general practice. From the brilliant young physicians whom he attracted to his department he was separated by an almost unbridgeable gulf. They belonged, in their hearts, to scientific medicine. They worshipped the gods of the machine and of the laboratory. They had never practised medicine in the homes of the people where they would be partners in the hopes and the fears, the difficulties and the triumphs of their patients, where they would learn the reactions of the child to illness from his earliest years and learn to foretell how he would react to the diseases that befell him in later years. They had tried to appreciate the viewpoint of Mackenzie but they had failed and there is much of pathos in the spectacle of the old physician—the beloved physician—who had for a time become the high

priest of the neocardiologists—leaving his disciples and returning to the field of work in which, he felt, lay his true vocation.

And so to St. Andrews where he founded the Mackenzie Institute, in which he hoped, with the help of local general practitioners, to study the earliest symptoms of disease. He appealed to the doctors of this cold, east-coast town simply as man to man and he won their wholehearted cooperation and support. He became consulting physician to the small cottage hospital which was staffed by the general practitioners of the town. For six years he inspired the family doctors around him in St. Andrews and indeed in all Scotland, for many came to visit the Institute and to seek inspiration and guidance from the founder.

One of my colleagues, when a young assistant physician, was sent by his chief with some slides of arteriosclerosis to ask Mackenzie's opinion about them. He tells me that Mackenzie just glanced at them and said: 'I know nothing about them, laddie, but come with me and I shall show you something I do know about'. He took him to his museum where he demonstrated the heart of a patient whom he had attended for twenty years and showed him where the disease had originated and how it had progressed. To this day my colleague regards that hour as the most memorable of his whole medical life.

At his weekly clinics, Mackenzie would demonstrate cases, oft-times stressing the presence of a symptom which his colleagues had either overlooked or misunderstood, and always he urged the need for constant observation and untiring watchfulness. He has said:—

'When I see the modern cardiologist getting his assistant to take an x-ray photo of the heart, an electrocardiograph and even a blood-pressure reading and then behold him sitting down to study these reports, I am truly amazed. I never could have realized that the practice of medicine would become so futile and ineffective. I must warn you against any immediate expectation of achieving the chief aim of medicine—the prevention and cure of disease. A long and weary road must be travelled and our immediate objective, after training ourselves in the detection of symptoms, is to find out the nature of these symptoms and, by watching patients over a period of years, to see what happens. It may be that, in this way, we may detect the causes and factors that favour the onset of disease'.

In the early days of 1921, he was compelled to give up active work, and by a sad coincidence, he who had done so much to elucidate the diseases of the heart was himself stricken by one of the most painful and hopeless of cardiac maladies. In the autumn he returned to London where, despite recurring attacks of pain, he completed the proofs of his last book—a review of the work of his cherished Institute and the new edition of 'Diseases of the Heart'. The figure of Death, so long defied, drew close to his side. There was one last seizure and then a period of peaceful sleep. On the night of January 25, 1925, the beloved physician went out quietly and serenely to his eternal rest.

What of the Institute which he founded? Like so many great men he had inspired no true successor. There was a gradual waning of enthusiasm after his death. The impact of the 1939-45 War scattered what he had regarded as a static population and made the keeping of accurate records almost impossible. To gather up the broken threads was deemed impracticable and the Institute has been closed down. The building is still there,

and I sometimes wonder whether we of the College might not one day find ways and means of continuing Mackenzie's work and fulfilling his dream.

A MEDICAL REVOLUTION

In the next two decades, discovery followed discovery with almost breath-taking rapidity. Insulin has enabled diabetics to lead a full and useful life. Liver extract and vitamin B_{12} have vanquished pernicious anæmia. Chemotherapy holds within bounds the dangers of infectious disease and the antibiotics enable us to triumph over almost all diseases of bacterial origin. We have indeed succeeded to a great heritage. We are living in the Golden Age of Medicine. We have today opportunities to practise the science of medicine such as our predecessors never obtained. The general practitioner has never had so many effective weapons in his armamentarium against disease.

With all these advantages, the lot of the general practitioner should be immeasurably improved, but is it? We are confronted with the psychoneuroses, the schizophrenias, the hysterias, the anxiety states, and the so-called stress diseases. Never were the people of Britain so disease conscious, so drug conscious, and so hospital conscious. In the creation of the Welfare State we have lived through a bloodless revolution. We have completely changed the character and the outlook of our people. We have had a great levelling up of things material but little improvement in the responsibilities which the up-grading should provide. Our Scottish poet, Robert Burns, sang of the desire to 'Gather gear by ev'ry wile That's justified by honour; Not for to hide it in a hedge, Nor for a train attendant; But for the glorious privilege of being independent.'

How many of our patients today wish to be independent? Do they not rather expect the State to guard them always against the slings and arrows of outrageous fortune? With the inception of the National Health Service we have had a medical revolution whereby every citizen is entitled to full medical care without any direct payment to his doctor or to the hospital. The citizen is now very conscious of the right which he can demand, but he oft-times forgets the duty which he owes to his doctor. The old order has changed and now the general practitioner is bound to his patient by the iron fetters of a legal contract enforceable day and night at the whim of the patient. Formerly the bond that united them was the golden thread of mutual esteem and confidence, and the obligation to render service was enforceable only by the conscience of the doctor. This has inevitably led to a change in the doctor-patient relationship not, perhaps, in a better direction.

THE RESPONSIBILITY OF THE STATE

We all realize that the National Health Service is a magnificent and humanitarian conception and none of us would wish to see it fail, but that sense of goodwill need not blind us to its many defects. The inception of the Service was unfortunate. It was introduced as a political measure and

was enforced upon an unwilling profession by a Minister who made it quite clear that he regarded professional people simply as workers with special skills, more elaborate, perhaps, but not so very different in kind from the skills of other workers. Indeed in Soviet Russia today the general practitioner working in polyclinics finds himself on the same social level as the woodworker or the motor mechanic. How different from Adam Smith who wrote two centuries ago:—

'We entrust ourselves and our health to the Physicians. Such confidence could not safely be reposed in people of mean or low conviction and their reward should be such as gives them that rank in society which so important a trust requires'.

It is not my intention to comment on the conditions of service or remuneration which we are 'enjoying' in the National Health Service today, but I do state unequivocally that the success or failure of the Service rests fairly and squarely on the shoulders of the Government. The State—not the doctors—introduced the scheme, and it is the duty of the State to ensure that the people of Britain enjoy a standard of medical care as satisfactory as is provided in other civilized lands. The doctors, though they accepted service with grave misgivings, to their eternal credit have given of their best to make the Service a success. Their wives too have sacrificed much of their social life and scanty leisure in an effort to maintain practice communications, very often without any domestic or professional help, and to them the people of the country and the politicians owe a debt of gratitude that can never be repaid. Without their aid the National Health Service must surely have inevitably foundered before it was properly launched.

THE NEED FOR UNITY

That all is not well with British medicine is evident from the many surveys that have taken place, from the articles that have been published, and from the letters written to medical journals. Both in general practice and in the consultant ranks, and more particularly in the younger age-group among whom the fires of enthusiasm should be burning brightly, a feeling of frustration, disappointment, unhappiness, and even despondency is to be found. Whether the particular type of nationalized medicine under which we work is the best for our Welfare State, whether it will maintain and enhance our scientific reputation or whether in its present form it will be to the ultimate benefit of the patient only time can show, but it is significant that few of our colleagues either in our own Dominions or in the United States would accept the conditions under which we work today. Particularly do they dislike the divorcement of the general practitioner from hospital, the political appeal to the cupidity of the public, and the capitation method of payment.

What then should we seek to attain in the foreseeable future? Our first objective should be unity in our own profession. The tripartite division into consultants, public health medical officers, and general practitioners, all under separate administrations, is an artificial segregation of the pre-

fession which can never work smoothly and with maximum efficiency. There should be no real demarcation between these three sections. We are all doctors with one common aim: to provide for the people of this country the best medical service within our means. In this objective we are all equal partners and it is my firm conviction that the good general practitioner is of equal value to the community as the good specialist. The divorcement between general practitioners and hospitals should be ended, and a limited number of keen and enthusiastic practitioners should once again become members and full members of the hospital team. Clinical clerkships which carry no responsibility are of some value, but they are not enough. It should be possible for the keen young practitioner to pursue for some years the specialty in which he is interested and, if he can obtain his higher qualifications, the fact that he has been part-time in general practice should be an advantage rather than a deterrent to his appointment to consultant rank.

In pre-National Health Service days, in the provinces many of our best consultants graduated from the field of general practice. Registrars should be encouraged to undertake part-time work in general practice with selected and knowledgeable practitioners. This two-way traffic will provide that personal contact between practitioners and consultants so necessary if each is to understand and appreciate the problems and difficulties of the other. It would also mitigate the difficulties encountered by those registrars who fail to obtain consultant rank and, as a second choice, wish to enter general practice. A scheme of this nature has already been agreed in principle in Scotland and the experiment when put into action will be watched with keen interest.

THE FAMILY DOCTOR

Is it possible to define in this socialized and nationalized era just what we mean by general practice? Platitudes such as the 'backbone of the profession', the 'front line of defence' may flatter, but mean little.

First and foremost we are family doctors and I should suggest that in the practice of medicine there must always be someone who can still take the broad view and the long view: someone who will see the patient as a whole and over a long period of years, who knows the common illnesses intimately and who knows when the rarer ones should be considered so that he can then summon to his aid one whose interests lie among these rarities. Even in this age, the family doctor cannot be by-passed. His place in our medical world is still supremely important. He must maintain a balanced judgment and use his own common sense. He must know his patients not as interesting scientific entities but as human beings, with their backgrounds, their families, their jobs, their virtues and their vices.

This is the man who can truly follow in the footsteps of Mackenzie, but for him the next decade will be a testing time and will determine whether he is to remain, as he has been through all the ages, a practitioner of the art, as well as of the science, of medicine or whether he is to be downgraded as a disposal agent for the nearest hospital. Against such a calamity our College

must be constantly on guard and vigilant. We must evolve some method by which the general practitioner will accept more and not less responsibility. We must encourage him to treat more illnesses in the home, and to undertake, as he so often did, even within our memory, simple diagnostic procedures and minor surgery. The public must realize that hospitalization is only for serious illness and that in their general practitioner they have a doctor who can deal with most illnesses just as skilfully as the 'professor' in the hospital ward. Much of the modern demand for hospitalization lies at the door of the politicians who instilled into the minds of the people that they were entitled to enter hospitals as a right whenever they wished to demand it.

To enable the general practitioner to give this fuller service will mean an increase in the number of Home Helps and District Nurses and may also involve a reduction in the size of lists with a commensurate increase in the fees payable. The saving in specialist services and hospital beds and the increased efficiency of the practitioners will more than offset these increased costs.

POSTGRADUATE EDUCATION

There must be adequate facilities for postgraduate courses. The average general practitioner has little leisure, but recreation and rest are as necessary for the doctor as for any other member of the community if he is to maintain efficiency. How often must he say, with Davies:—

> 'What is this life if, full of care,
> We have no time to stand and stare. . . .
> No time to turn at Beauty's glance,
> And watch her feet, how they can dance.
> No time to wait till her mouth can,
> Enrich that smile her eyes began.
> A poor life this if, full of care,
> We have no time to stand and stare'.

How difficult to find time even for recreation and reading! Yet with the advances in medical knowledge every year, to remain efficient a doctor must undertake postgraduate work at regular intervals. There must be no financial sacrifice incurred by the practitioner who takes a postgraduate course. A course for a month at a university city every fifth year might be envisaged. All fees, adequate subsistence and the full provision of a locum should be the responsibility of the State for those who work in the National Health Service. These courses should be arranged by the deans after consultation with representatives of the practitioners, and they should embrace all that is new in those diseases which are commonly met with in general practice. The student should also be taught how to recognize the earliest symptoms in the more uncommon diseases in order that he can make an early diagnosis and refer the patient to the appropriate specialist before the disease is too far advanced. There might well be occasional social and cultural meetings, more particularly in the evenings, when pupil and teacher could meet on common ground. Everything possible should be done

to make the postgraduate course memorable in the life of the practitioner. He should return to his practice with new knowledge, new friendship and a feeling of re-creation.

RESEARCH IN GENERAL PRACTICE

Any lecture which seeks to commemorate Sir James Mackenzie must take cognizance of research. Perhaps the most outstanding achievement of our College has been the contribution made to research by general practitioners in the past three years. Some hundreds of doctors are enrolled in the research register of our College and have been stimulated to observe, accurately and carefully, the signs and symptoms of the diseases in which they are particularly interested.

It is a sobering thought that we can give a complete and definite diagnosis in only about 30 per cent. of the patients who come to us for treatment. The others are only labelled with the name of their most prominent symptoms—neuralgia, headache, anæmia, constipation, dyspepsia—and if the symptom clears up with some simple medicament we pursue the investigations no further.

The world is too much with us and we say that we have no time, but for the lack of time we may occasionally fail to diagnose the early cerebral tumour or insidious carcinoma. Too often the word research conjures up in our minds intricate apparatus, spacious laboratories and a highly trained technical staff. What the word should mean for us is a spirit of inquiry, an effort to create a climate of discovery, a refusal to accept and to subscribe to current beliefs and teaching just because someone had postulated a hypothesis twenty or thirty years ago. As general practitioners, our concern is with clinical research. The beginning and the end of many diseases, treated for a time in hospital, are seen only by us. Only the general practitioner can properly evaluate the treatment given in hospital. The surgeon performs a brilliant and heroic operation from which the patient recovers sufficiently to return home but only the general practitioner knows to what extent that life has been crippled or renewed and whether the 'successful' operation has in fact been successful. Many illnesses which never require admission to hospital cause considerable incapacity. The psychogenic disorders, the anxiety neuroses so often produced by the whirl and turmoil of modern life, demand investigation by the general practitioner, but lack of time may preclude the taking of a detailed history and the patient may sometimes be sent away merely with a placebo for the nerves. How Mackenzie would have condemned such a travesty of treatment and how he would have insisted that we ascertain and endeavour to correct the underlying cause of these functional illnesses.

The capacity for work of the convalescent tuberculosis patient, of the epileptic, of the diabetic, can best be estimated by the general practitioner, who alone has the opportunity of watching the patient in his home environment over a prolonged period.

An opportunity for simple but valuable research work of this nature is open to every one of us. To those who complain, and there are many, of the lack of interest in the mass of trivialities that intrude upon the average consulting hour I would suggest that they develop a special interest in one subject, that they keep careful records of each case falling within that category and they will be surprised how alertness will increase and clinical acumen will be sharpened. Lack of secretarial help and lack of leisure constitute real difficulties but the satisfaction of finding some clue to the early detection of the disease in which we are interested, of searching for new evidence, of evaluating symptoms, of tentatively fitting a diagnosis—all this will give an uplift to our ego that far transcends the labour we expend.

REFORMING THE NATIONAL HEALTH SERVICE

We must strive to remove the National Health Service from the sphere of party politics. In association with the medical profession, all parties should seek agreement on the best methods of maintaining and improving the health of the nation. It is paradoxical that each year since its inception more money is poured out on the Health Service and each year more money is expended in sickness benefit and each year more working hours are lost through illness.

In New Zealand, after fifteen years of strife and bitterness, both political parties have come to an agreed solution of their differences and have joined with representatives of the medical profession to provide for the people of that great Dominion the best possible service for all sections of the community. In Canada, the politicians and the Canadian Medical Association are exploring the possibility of some form of compulsory health insurance but our colleagues there draw a very clear distinction between nationalized medicine and health insurance, the former, in their view, being a regimentation of the medical services by the State whereas health insurance means a pooling of financial resources by the prepayment of premiums whereby illness can be budgeted for in advance. They demand complete freedom of choice between doctor and patient, remuneration on a fee-for-service basis and they insist that any health service must be administered by an independent and non-political commission representing those providing and those receiving the services. With these principles, the politicians of Canada are mainly in agreement.

THE IMPORTANCE OF PRIVATE PRACTICE

So long as the health of the nation is used as a vote-catching instrument by the politicians, so long we, as doctors, must feel that we are mere pawns in the game of political chess. We may well wonder whether some day even our professional freedom may be undermined. To prevent such a catastrophe it is essential that private practice be maintained, not as a rival to the National Health Service but as a friendly competitor with it. The moment the State organizes and employs all the members of a profession we can no

longer regard it as a profession. We can only speak of a body of expert officials who might or might not be able to maintain their high standard of ethical conduct. These standards will depend upon the state of society—we have seen how low they could fall in Nazi Germany. Any freedom they enjoyed would be on sufferance from those above them who wielded the power. With the ever-increasing domination of the State over our day-to-day living it may well be asked: 'Will our traditional professional freedom be maintained after a few decades?' It is thus essential that some leavening of private practice should remain to safeguard our heritage and to keep in being a last citadel of freedom to which all can at need turn with safety and self-respect.

THE DOCTOR OF TOMORROW

The tendency of the State in all nationalized industries has been to depreciate quality when the services are overwhelmed by the sheer quantity of demand. At present we have an adequate—perhaps over-adequate—supply of doctors but already there is evidence that the new system is tending to attract recruits with a different background. In one Scottish University, only 5 per cent. of intending students came from medical families, and when these students graduate many of them seem to regard the practice of medicine more as a profession which enjoys a reasonable measure of financial reward rather than as a vocation.

EPILOGUE

In the Old Testament we read that Gideon gathered an army of 32,000 men to do battle against the Midianites.

> 'And the Lord said unto Gideon, . . . proclaim in the ears of the people, saying, Whosoever is fearful and afraid, let him return and depart. . . . And there returned of the people twenty and two thousand. . . . And the Lord said unto Gideon, The people are yet too many. . . . So he brought down the people unto the water: and the Lord said unto Gideon, Every one that lappeth of the water with his tongue, as a dog lappeth, him shalt thou set by himself. . . . And the number of them that lapped, putting their hand to their mouth, were three hundred men. . . . And the Lord said unto Gideon, By the three hundred men that lapped will I save you, and deliver the Midianites into thine hand. . . .'

Our College was founded as an act of faith in the future of general practice in Britain. Is it idle fancy, or may it be true to believe that those who are loyal members of our College, who are sincerely fulfilling the obligations which they have undertaken, are the men of Gideon who, in these years of difficulty and frustration, will uphold and perhaps enhance the high tradition of service that we have inherited from our fathers. To them in my dreams I can hear Mackenzie say: 'To you, from failing hands, I throw the Torch, be yours to hold it high'.

A VISIT TO THE U.S.S.R.

By IAN FRASER, D.S.O., F.R.C.S.

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MUCH has been written describing the organization of the medical profession in the U.S.S.R. In most cases the visits on which these have been based have been brief. The outlook of the writer may in some cases have been biased by his political spectacles, or by his narrow or personal interest in one branch of the subject. On occasion one has even felt that the report was written before the writer had left Britain. It is often said that to write effectively on Russia one must have lived there for twenty years or visited it for two weeks. My only justification for accepting the Editors' invitation to add to the literature on the subject is that I come into the second category. I was one of a group of six who visited four centres in the U.S.S.R.—Moscow, Leningrad, Kiev, and Sochi—for 21 days, during August 1956. The party consisted of two surgeons, two physicians, one radiotherapist, and a general practitioner.

HOTELS AND CAVIARE

The hotels where we were housed were first-class; some were twenty-storey buildings, and each bedroom had its own bathroom and lavatory. Cleanliness in the hotels was a noticeable feature in the bedrooms, corridors and dining rooms. Lounges, writing-rooms, or sitting-rooms are not a feature. There was always adequate hot water, but it is interesting that a plug for a hand basin did not exist in any of the hotels. All the baths were fitted with them, but not the hand basins.

Honesty was a marked feature in hotels and elsewhere. Parcels, money, and clothes could be left lying about with safety; a contrast to some other Capitals at home and on the Continent. Tipping does not exist, so one usually gives a present where real service has been carried out: e.g. to the chauffeur, who is at one's disposal from 9 a.m. until midnight; to the interpreter, who not only does the official interpreting but secures tickets for evening entertainments, such as the ballet, puppet show, or circus.

Food is excessive; the Russians eat a great deal. Breakfast especially can be a meal of any size, starting with a tumblerful of yoghourt, and a plate of white, brown and black bread. For protein there were plates of sliced ham, smoked salmon, sardines, with salads of tomato, raw onion, lettuce. This is followed by boiled eggs. The eggs are small, and two, three or four can be eaten; and on occasions this was followed by sausages and fried potatoes! On the table mineral water of the Vichy type was always available and a rather ersatz type of sweet lemonade. The mineral water was drunk in preference to ordinary water, a good deal of fluid being necessary with

the centrally heated rooms and the highly salted and flavoured food. Tea (Russian) and coffee (Russian or Turkish) were also available. Lunch most days was a snack lunch of much the same type of food, with the inevitable caviare, vodka and cognac, or sherry in deference to the lady visitor. It must not be assumed that we were not offered on some occasions champagne and vodka for breakfast also!

Caviare varied with the different centres. The best was the grey which is fresh, and unpasteurized; it will only keep for a few days and cannot be exported. The black was similar to that sold in Britain, and is just as expensive in Russia as in London. There was also the yellow or orange caviare, which varied in the size of the individual particles. It is looked on as inferior, and costs about one-quarter of the price of the black. The best black is the roe of the sturgeon; the yellow comes from the salmon or other allied fishes. The vodka was usually colourless, with the yellow type for very special occasions; it is expensive, costing about £3 a litre.

MOSCOW UNIVERSITY

A visit was paid to the new university built in four years and completed two years ago. As yet it only deals with a portion (9000) of Moscow's 22,000 students. It is a magnificent building of thirty-three storeys (fig. 1), standing on the Lenin Hills (formerly the Sparrow Hills), a vantage point from which Napoleon stood to watch Moscow (except the Kremlin) burning below him in 1812.

The individual rooms of this immense university are most impressive: large marble halls (fig. 2), with bronze busts, conference halls, library, and dance hall suitable for plays, concerts, and picture shows. The grounds are laid out in formal beds of neatly clipped flowers and shrubs reminiscent of Fontainebleau.

There are individual rooms for 10,000 students between the two universities. The students' bed-sitting rooms were excellent, usually in pairs, with lavatory and shower attached. There is much available ground around, so that the old buildings will eventually be replaced with the formation of an entire university colony. It is interesting that the main building is used so much as a hostel for the students and that the teaching buildings of the university are housed in large isolated units surrounding it. The new university contains the faculties of mathematics and mechanics, geology, geography, biology and soil, physics, and chemistry, whilst the old university, with its 7000 students, retains the faculties of law, philosophy, economy, philology, journalism and history. The remaining 6000 get their degree by correspondence. In addition to the 22,000 undergraduates there are postgraduate courses for 1,500 students.

In many cases on qualifying the students do not get a degree, just a certificate; they only obtain a degree after postgraduate study. Conferring day must be a dull affair; no brightly coloured gowns or hoods, just plain drab suits. The usual athletics are all catered for: association football,

basket ball, boxing, gymnastics, running and all track games, swimming, rowing, and there are suitable recreation rooms for the indoor sports so necessary in winter. Golf, cricket and rugby football have not been officially accepted as yet.

FIG. 1.—Moscow University.

THE MEDICAL CURRICULUM

In the university no faculty of medicine or dentistry exists. This has been so for the past twenty-five years. There are in all perhaps thirty universities in the U.S.S.R., and with the rapid increase in the number of doctors required it was necessary to arrange another method of instruction and so there now exist seventy autonomous medical institutes. This has allowed a wider distribution of these training colleges over the vast area of the U.S.S.R.—one-sixth of the surface of the globe—and the doctor in the most remote areas obtains his training locally. At first sight it seemed sad to think that the medical student was no longer a member of the university, but if we ask a London medical student where he trained, he will say Guy's, Bart's or Thomas's, and will look on his link with the London University as a very tenuous one indeed; and the same is happening in the majority of British universities.

This fact, however, is accentuated in Russia, where all the students are supported by the State, and as this includes their accommodation as well as the teaching fees it does mean that the Institute must put up sufficient residential quarters. The rooms may be single or double. The sexes may

FIG. 2.—The main entrance hall, Moscow University.

live in a communal residence, and if they get married they can live together. About one-third are married by their fifth year, and for those who have a family there is a crèche attached, and naturally there is a polyclinic which looks after the university students' health problems.

In British universities there is just one medical faculty, as the students, no matter what their future intentions may be, all do the same course for six years until qualified, and after that they may divert to the specialty of their choice. In the U.S.S.R. there are three alternatives before the young prospective medical student, which he must choose before entering the medical institution. They are:—

(1) He may take a general training. This can lead to his specializing later, but if he does not specialize he will be trained to become a fully fledged general practitioner.
(2) He may choose to be a pædiatrician.
(3) He may choose to be a sanitary or hygiene expert.

Thus all institutes can have three separate faculties; in actual fact most have only two. In a few a fourth faculty is added and that is dentistry or stomatology. In the 1st Moscow Medical Institute there are two faculties: one is general training and the other sanitary health. In the 2nd Moscow Medical Institute there are also two faculties, but one is general training and the other is pædiatrics.

In the 1st Moscow Medical Institute there is a yearly intake of 500

students: 250 for each faculty. Every facility is given to a student to change to the general training faculty but not so much the other way. The failure rate is very small. There are two reasons for this. In the first place, competition to get into the Institute is very keen: there are perhaps 17 applicants for each single vacancy. Secondly, the candidate is supported by an impersonal State that will stop his allowance immediately if he fails, as compared with the indulgent parent who is to be seen in other places. The total failure rate is about 10 per cent.

The intake of women is 75 to 70 per cent. This may seem very large; it is partly the result of the war, when women were more available with so many men away fighting, but ever since the war the numbers have not gone down. This figure must not be compared with the 18 per cent. in British medical faculties, but rather with the ratio of women in other types of employment in the U.S.S.R.: e.g. agriculture and factories. Thirty-five per cent. of engineers in Russia are women and some are outstanding. Is it possible that Britain is losing valuable possibilities by having so few women engineers?

The average student has seven years in an elementary school, and three years in a secondary school, so that he is 16 or 17 before leaving school (not less than 16 by order of the State). The medical curriculum for all three faculties covers six years of study. The first two years is a course of anatomy, physiology and allied subjects, which is common to all three faculties. At the beginning of the third year the training develops into the specific specialty. At the end of six years the student is a 'graduate', but not a doctor. The latter title can only be achieved by postgraduate training.

The student would appear to have a closer eye kept on his work. With frequent short oral examinations and constant survey of his last reports it would be difficult for a student to slack all year, and only be discovered at the final term examination. In fact, the final examination is entirely oral; there is no written paper.

So far as holidays are concerned the students get two weeks in January and two months in the summer. Many go off hiking or on geological and archæological expeditions. About 1000 students go to the collective farms during the holidays.

MEDICAL STUDENTS

The students all give one the impression of being young and immature. Although almost all the men smoke, less than 1 per cent. of the women students do, and for a woman to take alcohol at any age is looked on with great disfavour. Nail varnish seemed to be used by one out of every 100 to 200 students, and lipstick by one in 50 students. There is a great earnestness and seriousness. It would be hard to visualize a students' rag, or the rough house that can develop at a medical students' dance. A new professor, I feel, is rarely subjected to the indignity which is now looked on in Britain as essential for his initiation. Libraries and reading-rooms abound. They say there are sufficient reference books available, but the student must buy

his own notebooks. Although meals are taken in a communal restaurant, there are facilities in small kitchens where unofficial meals can be made. The chess rooms that are present in numbers are in keeping with the general serious attitude.

Although art, bright colours, ornate gardens, elegant buildings and a love of ballet abound and are fostered by the State, the same degree of art does not appear in the dress of the Soviet citizen. The women are dowdy; garments are drab, not well fitting, and no garments seem to be worn to keep the female figure in check, so that at first glance one gets the idea of a high percentage of pregnancy, which is not so. The students' quarters are fitted with telephones in the corridors, a wireless set to each room, and television freely available. Television abounds in Moscow, and the flat roofs of the apartment houses bristle with aerials.

MEDICAL MAN-POWER

Since the student is supported for his six years of training at the expense of the State it is only rational that he has to give something in return. He is obliged to give the first three years after that to the State and for this time he may be posted anywhere. It is a form of national service. With the wide distribution of the medical institutes from Leningrad to Vladivostok the hardship is greatly reduced. It is interesting to note that there is a more or less universal salary for professors, whether they are at the seat of learning in Moscow or in Siberia. This is in contrast to other spheres of employment. The worker on the railway in the frozen north, for instance, gets a considerable increase for hardship, so do those who have to work in the intolerable heat of Tashkent.

In the United Kingdom, with its densely packed population of 50,000,000 and its many universities, a state has been reached where we have a doctor for every 600 of the population. In the U.S.S.R., with 200,000,000 inhabitants, and a surface area covering one-sixth of the surface of the globe, the same ratio is said to have been reached: one doctor for every 600 people. This is most creditable when one thinks of the vast areas of Siberia.

POLYCLINICS

Man-power is less wasted in the U.S.S.R. The family doctor acting on his own in a small isolated area, as we know him in this country, does not exist. Instead they work in groups. An area is divided up, as indeed we did during the last war, when we worked out the necessary doctors, hospital beds and the like, necessary for thousands of troops, the figure naturally depending upon whether the area was at risk, at peace, or in an epidemic area. In the Russian towns polyclinics are provided, manned in proportion to the size of the district. The one we visited was responsible for the entire health of a section of Moscow of 32,000 people. A doctor from the polyclinic could go to see the very ill patient, e.g. with perforated duodenal ulcer or coronary thrombosis, but no constant home visiting could be

undertaken. Most polyclinics have a few beds for the not very ill, but the really serious case must go to hospital. In some cases the polyclinic was attached to a hospital. This had much to be said for it, as the staff could call on the senior consultant staff, and the professorial staff could use the patients for teaching purposes. The polyclinic is little more than a health centre which has been converted into a multiple diagnostic outpatient department. It naturally takes in all the specialties but differs from the outpatient department of the general hospital at home in that it has such a large general-practitioner department as well.

From the doctors' point of view this system has much to be said in its favour. The doctor is working with his colleagues all the time and has a second opinion always available. Consultations are all by appointment: four or six to the hour. The doctor has a seven-hour day, but if he wishes he can have another State appointment which naturally brings him in an additional income. This is welcome in the U.S.S.R., where income tax is minimal. A married pair without a family may have to pay 3 to 4 per cent. income tax, but this is reduced as a family arrives, until, with two or three children, no income tax is payable. If the marriage is childless and the wife has reached 40, or the husband 55, a generous State reduces the income tax as the childless condition must then be due to infertility.

SURGICAL RESEARCH

All the medical institutes have a large research department. Pavlov's ghost can be seen everywhere. Their surgical experiments were most interesting in some cases, but what value will arise from them was not clearly visible.

In one unit, for instance, they had removed the hind legs from dogs and immediately replaced them: i.e. plated the femur, reunited the veins and arteries with the special vascular suture machine, and sutured the sciatic nerve. We saw these dogs three months after this procedure walking with a limp, and after six months or so bounding along and jumping for food. Another experiment was to place a second heart in a dog's thorax to act in series with the existing one. Another was to anastomose the internal mammary artery in dogs into the right coronary artery. We saw a series who had had this done some years ago, but what a difference there is between anastomosing a healthy artery into another healthy artery in a young greyhound as compared with the arteriosclerotic vessel in an ischæmic heart of an elderly human patient. The operation was just as irrational as O'Shaughnessy's had been.

We also saw a film of rather a disgusting experiment. The first section showed two dogs playing. In the next section the head and shoulders from one had been cut off and implanted into the neck of the first dog. Vascular connexions with the brain of the second head had been linked up. When offered milk both heads were able to drink, but from the parasite head the milk escaped from the cut œsophagus, and the parasitic trachea had not been linked up with that of the main animal. It was a clever piece of dexterous surgery, well carried out, but where does it lead us? It was interesting that the parasitic graft lived at all, as skin grafting as we know it in human beings is restricted, if successful, to identical twins.

The professors we found most willing to show us everything; in fact, our greatest difficulty was to try to keep to a time schedule, and this we failed to do on many occasions. More than once our first host kept us until well after the time of our second appointment, with disastrous results

occasionally, particularly if host No. 2 had arranged an operation; e.g. a valvotomy so timed that we would arrive at the critical moment. This did happen on another occasion. The professor of neurosurgery had four operating tables all going, and at 11.30 hours, when we were due to arrive, he had hoped to flit like a prima donna from one to another to remove the tumours. We arrived one hour late, but he still did as originally arranged, taking seventy minutes to do all four cases—but the cases had been kept waiting for a very long time.

SURGICAL TECHNIQUE AND ANÆSTHESIA

Local anæsthesia, 0.25 per cent. novocaine in very large quantities, is the main anæsthetic employed. It can be given in quantities of as much as 1,100 millilitres. This large volume is administered by either a rapid change of 10-ml. syringes, or, in a few cases, by the continuous syphon type of syringe. The pressure alone of such a large volume reduces the actual amount of bleeding. Spinal anæsthesia is also used. In many cases there is a stand-by general anæsthetist. This is called for in children, and also for the highly nervous.

One professor we met does all his heart and lung cases under local anæsthesia. I saw him remove a large neurofibroma from the upper mediastinum in a young woman of 30.

The tumour, the size of an orange, was difficult to approach, being close to the hilum of the heart. To reduce the disturbance of entering the chest he did a pneumothorax the night before. He also infiltrated the posterior surface of the carotid sheath, claiming thereby to affect the sensory fibres of the vagus without any involvement of the motor portion. A long incision was made under the breast, followed by infiltration of three intercostal spaces, and then an intercostal incision with cutting through of the costal cartilages in front to allow access. Infiltration of the pleura and pericardium and depression of the upper lobe of the lung allowed the tumour to come into sight.

There is no doubt that there is more mental anxiety for the patient, and for most surgeons local anæsthesia is more physically wearing. The same surgeon showed us an excellent colour film of his operation of valvotomy in a girl of 18, all under local anæsthesia. Surely there must be some anxiety to the conscious patient to think that the surgeon has a finger in the centre of her heart.

Although great stress is laid on the fact that 80 per cent. of operations are done under local anæsthesia, and we were given to understand that in many cases local anæsthesia was the method of choice, we did find that thirty of Mackintosh's apparatus had just been bought, and Mackintosh himself has since been out to give practical instruction in their use.

One surgeon interested in thoracic work did all his lung operations, thoracotomies, thoracoplasties, lobectomies and pneumonectomies, under local anæsthesia, but preferred general anæsthesia for his heart operations. He had just completed a large book on congenital abnormalities of the heart. He showed us a large series of valvotomies. He divided his cases of mitral stenosis into five groups:—

Group 1, with minimal symptoms. In his opinion these should have the operation,

but his physician colleagues will not pass them on to him. Group 2, dyspnœa on exertion; these he operated on with a small death rate. Group 3, dyspnœa at rest, and œdema; these had a larger death rate. Group 4 consisted of cases too ill for immediate operation; in these he finds that to do a preliminary ligation of the inferior vena cava through a transverse incision at the level of the umbilicus reduces the congestion and on these he is able to do a valvotomy some months later. Group 5, bedridden; inoperable.

We saw a recent case of coarctation of the aorta which he had excised and replaced with a graft of three inches. He had not done any aortic valve operations or intraventricular septal defects, except in the experimental animal.

The ancillary apparatus in this surgical cardiac unit was first-class. Electrocardiographs of all sorts, many of beautiful workmanship, some of Russian manufacture, others from Turin. The only non-working piece of expensive apparatus that we saw was an extracorporeal heart-lung apparatus sent out from a London firm, with certain parts missing and quite unusable —a sad reflection on British workmanship.

We saw two entirely different pieces of apparatus for arterial suture. On both occasions, a dog was brought in with its carotid artery severed and re-anastomosis was carried out while we waited. A most ingenious piece of surgical apparatus not yet on the market was an advance on the Petz clamp or so-called ' sewing machine' for closing the stomach or bowel.

In the Russian instrument there were two blades on the upper end of the viscus. On closing the first blade a row of silver staples was put in; by turning a further lever, inversion of the edge took place into the cavity of the stomach or other organ, and the second row of staples was inserted, so that with two manipulations the bowel was cut through and closed in two layers with complete inversion.

Yudin, reinstated just before his death as the leader of Russian surgery, has an annual eponymous lecture named after him. He is chiefly famous for 10,000 gastrectomies, and for the fact that of the 800 œsophageal replacements that have been carried out at his hospital some 350 stand to the credit of Yudin himself. One such case was put on for our benefit.

It must be remembered that an œsophageal operation in Britain means in the first place removal of the diseased œsophagus from its mediastinal bed before replacement takes place. In Russia the operation is most often performed for complete stenosis due to the swallowing of caustic, and so the new œsophagus can be made while the disused one remains for ever *in situ*. The new tube can be a skin tube lying in front of the sternum. It can be an isolated segment of upper small intestine still well fed by its blood supply from the superior mesenteric artery which also can be brought up subcutaneously in front of the sternum and joined to the œsophagus and pharynx in the neck and to the stomach in the abdomen; or it can be an isolated segment of small bowel taken through the pleural cavity behind the sternum, joined again to the stomach, if technically possible, at the lower end, if not to the duodenum, and to the pharynx or œsophagus at the upper end. The upper end is made to traverse the chest and emerge through Sibson's fascia at the root of the neck. The final anastomosis at the upper end is made after a delay of four days. In the event of the upper end of this graft having an inadequate blood supply the internal mammary artery has been used to bring additional blood to it by anastomosing it to one of the branches.

This operation we saw carried out in a young man of 19 who had accidentally swallowed caustic at the age of 12, and for seven years had been fed through a gastrostomy opening. The operation was carried out under

spinal and local anæsthesia; the operator passed his hand through the right leaf of the diaphragm and guided the upper end of the small intestine segment to the apex of the pleural cavity, where it was exposed through the neck. The operation, having been done so often, must be effective, but certain points give food for thought. The piece of gut when taken through the diaphragm was in no way sutured to the diaphragm; its blood supply was already precarious, and any constriction would have been dangerous, and we did wonder about a diaphragmatic hernia. It was a formidable procedure, and the young man stood up to it with great courage. The operation took about ninety minutes.

A round of a surgical ward showed that the type of case was much the same as in any British hospital: goitres, hernias, factures, hæmorrhoids, amputation of the breast, gastric operations for ulcer and cancer, operations on the biliary passages. Gastrectomy was mostly of the Polya-Hofmeister-Finsterer type. Vagotomy alone had been tried, as in this country, and discarded; even associated with other operations it no longer seemed to be used. For the perforated ulcer the type of operation depended upon the status of the hospital and skill of the surgeon. In one small hospital closure of the perforation was all that was done. In a large teaching unit the majority had an immediate gastrectomy—in fact, this was the rule except in young patients, or the very old. Gastric suction, and intravenous replacement of fluids or blood were carried out as at home.

BLOOD TRANSFUSION

Blood transfusion is well organized, and Leningrad had a specialized unit for this purpose. Attached to the blood transfusion service was a specialized hospital for 60 beds for treatment and research into the rare and dangerous types of blood disease. Blood transfusion is treated with greater ceremony than at home. Donors give only 450 ml. at a time, and may be used up to six times a year. They must be between 19 and 50 years of age. Great care is taken in their selection. The chest is x-rayed, and the blood examination includes white cell and red cell count, blood group, serum bilirubin, malaria, and Wassermann reaction. Any suggestion of disease, e.g. hypertension, disqualifies the donor. A transfusion takes two days, and the donor is allowed off work with full pay for two days. The first day is for a check-up and the second day for taking the blood. The donor has a complete bath or shower, and is then dressed in white shirt and trousers. He then mounts the stairs. This and the passageway are irradiated with ultra-violet light. He enters a small room, lies on a trolley, and puts his arm through a hole in the wall (like the ticket office at a railway station). His arm reaches through into a room, again irradiated with ultra-violet light, and from there with aseptic technique the blood is taken. This room is air-conditioned and air-tested.

They say that the donors are all voluntary, but for each session of 450 ml. they get 250 roubles. This is meant to enable them to buy extra rations.

They also get a badge of distinction. In Leningrad all donors come to the centre. There is no peripatetic van to go round the factories. Intervals of blood-giving are strictly controlled; the maximum is six times a year; in practice, it is usually two or four times. A further incentive to be a blood donor is additional holidays; e.g. a donor who has given blood five times will get five days' extra leave. Some of the star donors, e.g. of the siege of Leningrad, are used for propaganda purpose, and have special holidays. The State is said to have spent up to 250,000 roubles on sending these stars on holidays.

CADAVER BLOOD TRANSFUSION

Cadaver blood transfusion is mainly centred in one hospital—the accident hospital in Moscow. The original work was started by Shamov (now neurosurgeon in Leningrad), who did his early research work in dogs in 1928, but it was Yudin who, in 1932, used it first—in a case of suicide. After a slow beginning, in a few years it was an accepted treatment, and in twenty-five years they have used 25 tons of cadaver blood without trouble. The advantages claimed are that for a large transfusion, e.g. of 4 to 5 pints, the total quantity can be obtained from the same source rather than five sources with all the possibilities of incorrect matching and the like. In fact, all that is against it is sentiment. The case chosen is selected with greater care; a full post-mortem examination is carried out. With the slightest suggestion of disease in the cadaver, the blood is thrown away. In fact, the best cadaver obviously is the healthy young adult killed in a street accident.

Even in the accident hospital, however, fresh blood is widely used, but, as they say, there is little difference in blood taken from a man or taken from the body within six hours of death, and with the latter, with a full post-mortem examination, one is more sure that the blood is coming from a pure source. Sentiment and religion, however, come into the picture and when Yudin published his paper in France in 1934 there was a great outcry, headed by the Pope, so that its use was forbidden in France.

HOSPITAL WARDS

The wards in all hospitals were overcrowded to our way of thinking, but perhaps the Englishman is too sensitive about his privacy. Oxygen was laid on to many beds, and ear and pillow phones were always available. There was more space available for the up-patient than in Britain, and more food was taken at small tables than in bed. So far as one can see there is virtually no waiting list for admission—this is at the price of overcrowding. In Russia it would appear that sufferers from piles, or varicose veins, get into hospital at once, with the discomforts of overcrowding and lack of privacy, whereas in this country after waiting perhaps eighteen months, they have the operation in comfort, luxury and privacy (if still living). Great Britain has practically 500,000 people on the waiting lists of hospitals at present. In this we see the different ideologies of the U.S.S.R. and Britain.

CURRENT THERAPEUTICS

CIX.—THE PLACE OF BZ55 (CARBUTAMIDE) AND ALLIED COMPOUNDS IN THE TREATMENT OF DIABETES MELLITUS

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THE discovery of insulin and its importance in the treatment of diabetes mellitus early stimulated the search for an oral substitute. Lewis (1949) reviewed the efficacy of all the oral preparations that had been used in the treatment of diabetes mellitus. The most effective was synthalin but even this preparation had marked toxic effects upon the liver and nothing like the degree of hypoglycæmic activity of insulin. Last year, Loubatières (1955) reviewed the use of sulphonamide preparations as hypoglycæmic agents and drew attention to the earlier work of Janbon *et al.* (1942) on the hypoglycæmic action of *p*-aminobenzenesulphonamido*iso*propylthiodiazole (I.P.T.D.)

Clinical attention was recently drawn to the possible therapeutic value of *N*-butyl-*N'*-sulphanilylurea (BZ55; carbutamide; 'invenol'; 'nadisan') (fig. 1) by the publications of Franke and Fuchs (1955), Bertram, Bendfeldt and Otto (1955), and Achelis and Hardebeck (1955) on the successful control of the majority of their middle-aged or elderly patients suffering from mild diabetes mellitus. Many experienced clinicians in other countries considered that the patients selected by the German workers were examples of the obese and mild type of diabetes so often successfully treated by dietary restriction without resort to insulin and the beneficial therapeutic effect might have been ascribed to the increased professional interest and to the consequent better supervision.

During the past year numerous reports have been published in Canada (e.g. Charles, 1956; Metzler, 1956; Watt, 1956), the United Kingdom (Duncan *et al.*, 1956a; Hunt *et al.*, 1956; Murray and Wang, 1956; Walker *et al.*, 1956; Wolff *et al.*, 1956) and on the Continent confirming the hypoglycæmic action of BZ55 and of another compound: *N*-butyl-*N'*-toluene-*p*-sulphonylurea (D860; tolbutamide; 'orinase') (fig. 1).

MODE OF ACTION

The known toxicity of sulphonamide preparations, particularly their effect upon hæmopoiesis, hepatic and renal function, has stimulated a considerable number of investigations into the mode of action of these preparations, and Young (1956) recently reviewed the pharmacology of the antidiabetic sulphonamides. Initially the Germans claimed that BZ55 had a direct action on the alpha cells of the islets of Langerhans, causing their destruction and in consequence a reduction in the secretion of glucagon. This view has not been satisfactorily confirmed although some workers have noted changes in

the alpha cells. The major action of BZ55 suggested by Mirsky *et al.* (1956), namely that the sulphonamide preparations suppress the catabolism of insulin by acting as non-competitive inhibitors of the liver insulinases, is now generally accepted. There is also evidence that BZ55 may have a stimulating effect on the beta cells, leading to an increased secretion of insulin (Ashworth and Haist, 1956). Clinical studies by Duncan *et al.* (1956a) and others in this country indicate that the effect of the antidiabetic sulphonamides is to depress the blood sugar throughout the twenty-four hours without altering the intra-daily pattern. In patients treated with BZ55 the glucose tolerance test has a similar form to that before treatment but throughout the blood-sugar level is depressed, the degree of depression varying to a certain extent with the mean fasting blood-glucose concentration.

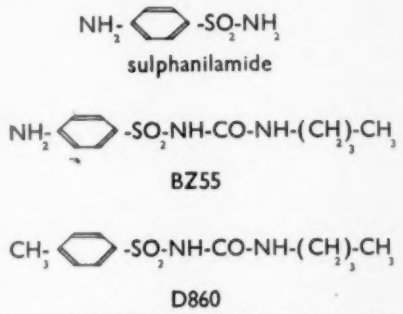

FIG. 1.—Chemical formulæ of sulphanilamide, BZ55 and D860.

Comparison of the mean fasting blood-sugar values before and after the administration of BZ55 gives definite evidence of the depressive effect of the preparation on the blood-sugar level. Every patient did not respond to the preparations but Duncan and his colleagues are of the opinion that the response of the fasting blood-sugar level gives some indication of the likelihood of clinical success from therapy. The blood sulphonamide levels have been estimated by the method of Bratton and Marshall (1939) in an attempt to correlate the blood sulphonamide level with the hypoglycæmic effect. It was found that in any given patient the blood level of BZ55 remained remarkably constant but there was considerable variation from patient to patient and the absolute value bore no relationship to the hypoglycæmic response. Further, there was no fundamental difference in the blood values for sulphonamide in the patients who responded successfully to treatment and in those who were resistant.

Attempts have been made to devise a test which would indicate the likelihood of successful therapy. As already mentioned, Duncan and his colleagues consider that the depression of the fasting blood sugar is a good indication of the likelihood of a successful response but that it is by no means an absolute guide. Several other workers, notably Mirsky, have utilized the six-hour response to a given dose of BZ55. Dr. B. H. McCracken, working in my Department, has utilized this test and has found, as shown in fig. 2, a varying response. The patients who do show a definite depression of blood sugar with this test, particularly when the depression occurs at the latter part of the test, that is to say between the fourth and the sixth hour after

administration, form the group most likely to respond to therapy. Thus, we have no reliable test to indicate with certainty how a patient will react but there is certainly a place for estimating the effect upon the fasting blood

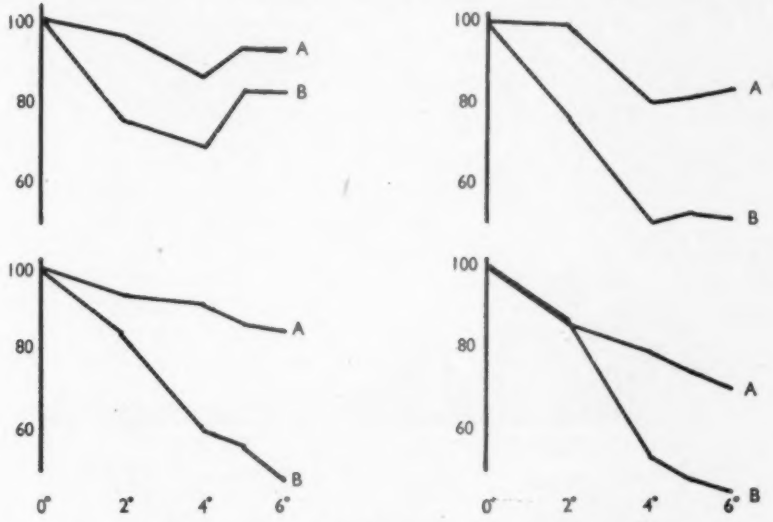

FIG. 2.—Blood-sugar levels in six-hour test. A = control. B = after BZ55. Abscissa = percentage depression of fasting level. Ordinate = hours.

sugar and also for using the fuller test by observing the response for six hours after the administration of a dose of 2 g. of BZ55, or 50 mg. per kg. body weight.

CLINICAL RESULTS

The German workers now claim to have treated nearly 2000 patients, and over 1000 for more than twelve months. They do not advocate that BZ55 is suitable for the treatment of all patients but have confined its use to the treatment of mildly obese middle-aged or elderly patients who obviously had been on only a small dose of insulin and were not liable to ketosis. The more recent reports in this country, Ireland and Canada are in agreement with these general conclusions. Many patients previously on insulin, although the dose was small, have developed ketosis when placed on BZ55 and the latter has been quite incapable of controlling the carbohydrate metabolism in such circumstances. There is general agreement that the preparations are virtually ineffective in subjects liable to ketosis. Numerous attempts have been made to use BZ55 in combination with insulin, particularly in patients known to have wide fluctuations in the blood-sugar level and particularly those liable to develop a considerable degree of hyperglycæmia during the early hours of the morning: that is to say between

4 a.m. and 7 a.m. In general, little success has been obtained with combined therapy in patients who are receiving initially a total of more than 40 units of insulin a day.

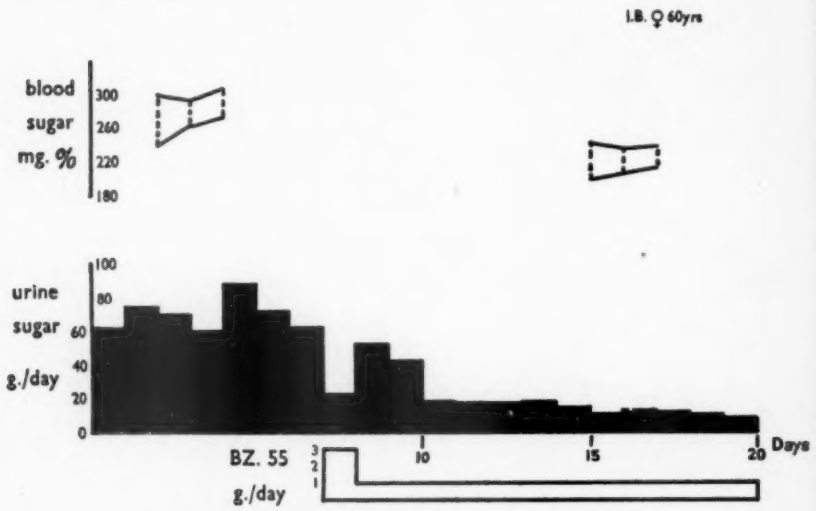

FIG. 3.—Response of a patient, aged 60 years, to BZ55.

The German workers have stressed the success of the preparations in the treatment of obese patients. The recent reports from Great Britain would indicate that success may be obtained in patients whose body weight is within normal limits. In fact some of the most successfully treated cases have been patients with normal body weight and a tendency to hyperlycæmia but not to ketosis (fig. 3). Wolff (1956) has had the opportunity to treat a patient following pancreatectomy and the preparations appeared to be without effect. Most of the reports in the literature relate to comparatively short periods of treatment, six months or less, and there have been very few reports on the long-continued treatment of patients with either BZ55 or D860. There is some evidence that patients responding initially may fail to maintain the response even when the dosage of BZ55 is increased.

Various dosage schedules have been used. Most workers have used an initial dose of 2 or 3 g., followed by a daily dose of 1 g., reducing the dose in some instances to 0.5 g. a day. Some patients have required a dose of as much as 2 g. daily to maintain the effect but the risk of toxic reactions has led to extreme caution in the use of such a high dosage.

TOXIC REACTIONS

The original German work suggested that very few toxic reactions had been obtained, mainly skin lesions, and one case of jaundice for which there was an alternative etiology. Nearly all the reports from North America and from this country stress the frequency of toxic reactions: the most common are

the dermal reactions, the incidence of which varies but has been as high as 15 per cent. in some series. The skin reactions have shown the usual variety one has learned to associate with sulphonamide sensitivity, and in some instances have been accompanied by drug fever.

Still more important and striking has been the responsiveness of the hæmopoietic system. Routine examination of the platelet count after the administration of BZ55 revealed a high percentage of patients exhibiting a depression of the platelet count. Cessation of the drug is followed by a rapid return to normal. Further administration of the drug is followed by a similar response, the degree of fall may be anything from 30,000 to 100,000 platelets per c.mm. In some cases, with long-continued therapy the platelet count returns to within the normal range of values. Two cases of spontaneous purpura have been reported and a number of cases of persistent thrombocytopenia, all following the use of BZ55. There is a suggestion in the American literature that there may have been three fatal cases of agranulocytosis following the use of BZ55. It is for these reasons that four clinicians experienced in the treatment of diabetes mellitus have felt it necessary to issue a warning that the use of BZ55 was not without considerable risks (Duncan *et al.*, 1956b).

Intense headache and depression have also been noted following the use of BZ55. These symptoms rapidly disappeared on cessation of treatment.

So far there is no report in the literature of renal complications. This may be due to the method of excretion of the preparation which, in the dosage used, would render it unlikely that there would be a sufficiently high concentration to cause crystal formation.

DISCUSSION

Experimental and clinical evidence has confirmed the claims of the German workers concerning the hypoglycæmic effect of BZ55 and D860 in man. The high incidence of toxic symptoms with the former is an obvious and serious contraindication to the use of this compound. The development of late toxic manifestations and the diminishing response to the action of BZ55 with time in some patients are further contraindications to the use of this preparation, even for the mild elderly hyperglycæmic and non-ketotic diabetic. The use of BZ55 is definitely contraindicated in unstable diabetics and in all diabetics liable to ketotic episodes. Theoretically, owing to the substitution of the amino group by the methyl group, D860 should be less toxic than BZ55, and the present medical evidence would appear to confirm this, for fewer dermal reactions, and a lessened incidence of platelet depression, have been observed, but, as the preparation has not been in use as long as BZ55, it would be unwise to form a premature judgment.

Even in the potentially suitable case—the mild, relatively stable hyperglycæmic diabetic receiving no insulin, or only a small dose of insulin—it is impossible to predict the effect of sulphonamide preparations without a trial. It is advisable to determine the six-hour hypoglycæmic response to a

fixed dose, or to determine the effect on the fasting blood-sugar level before instituting therapy. It must, however, be clearly understood that even in patients responding to these tests it does not follow that they will necessarily respond to long-term therapy. In view of these facts it seems essential that all patients selected for treatment with BZ55, or D860, should be admitted to hospital in the first instance.

CONCLUSION

These preparations have no place in the routine treatment of diabetes mellitus, the treatment for which still consists in dietary restriction and in some 50 per cent. of cases the addition of insulin.

The risks of sulphonamide therapy in the limited number of cases suitable for such treatment outweigh the potential benefits.

The main value of the discovery of the hypoglycæmic reaction of BZ55 and D860 lies in the stimulus given to research into the mechanism of the action of insulin and the abnormalities of metabolism occurring in diabetes mellitus.

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EQUIPPING THE SURGERY

I.—SUTURES AND SURGICAL INSTRUMENTS

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In Britain major surgery is done only in hospitals, and usually by specialist surgeons. The family doctor, however, is called upon to undertake the primary surgical treatment of accidental injuries, to stop hæmorrhage, to suture wounds and to extract accessible foreign bodies. He also undertakes minor operations such as the removal of cysts or superficial blemishes, the opening of subcutaneous abscesses, and circumcision. For this he needs a simple equipment of instruments and materials.

INSTRUMENTS

(Fig. 2-3)

The selection of instruments will naturally vary with the practitioner's previous training and his personal inclinations, but the following will probably be required. As they are often boiled, stainless steel instruments should be chosen in preference to plated ones.

Razor.—A safety razor is soon clogged and the old 'cut-throat' razor comes into its own in shaving a hirsute limb.

Knives.—The modern surgical knife of the Bard-Parker type with detachable blades, is almost essential.

Two *handles* will be needed:—

No. 3 for small blades.

No. 4 for large blades.

Four *blades* will be found useful:—

No. 22 (or 20), round bellied, large. For most surgical work.

No. 15, round bellied, small. For delicate work on the face.

No. 11, sharp pointed, straight.

No. 12, sharp pointed, curved. For opening abscesses.

Dissecting forceps.—Two pairs are recommended. The toothed type are needed for surgical work. The six-inch size is the most useful. The non-toothed type, supplied in most dressing-cases, is useful for picking up dressings and for blunt dissection, but almost any other instrument will do these jobs just as well.

Scissors.—Two pairs at any rate will be needed; sharp pointed for removing stitches; blunt pointed for most other work, and for dissecting in areolar planes. The most useful are curved scissors of the Mayo type.

Artery forceps.—Half-a-dozen six-inch 'Spencer Wells' of the Mayo pattern, or four six-inch 'Mayo' forceps and two four-inch 'mosquito' forceps.

Tissue forceps will be required for holding the edges of a wound. Two pairs should be enough. The Lane six-inch pattern is more durable than the more delicate Poirier or Allis types.

Needle holder.—Many types are available, but one such as the Lane, that has the standard finger grip of a surgical instrument, is probably preferable.

Sinus forceps.—One six-inch pair. This is a dressing rather than a surgical instrument, but has many uses, chief among them the insertion of a rubber strip for drainage.

Probe.—A silver probe, being malleable, has many uses. A combined grooved director and aneurysm needle is also a handy instrument. Both are cheap and should be included. A metal crochet hook for extracting stitches from the bottom of a sinus, is also useful.

Blunt spoon.—One of these instruments, with a spoon of different size at each end, is useful for getting the dirt out of the lacerated wound of a road accident, and occasionally for scraping away granulations.

Retractors.—A couple of small retractors (such as Durham's fenestrated), with blades about $1\frac{1}{2}$ inches deep and $\frac{3}{4}$ inch wide, will be found useful. For small jobs the aneurysm needle, or bent probe, serves well.

STERILIZATION

In any surgery a small sterilizer is an absolute requisite, and the 11-inch size is convenient (fig. 1). An electric sterilizer is most suitable for the consulting room, but many practitioners like to carry a spirit-lamp sterilizer for emergency work.

The question of syringe sterilization is a difficult one. Many practitioners still rely on spirit sterilization, but this is not wholly reliable, and legal play might be made of its defects if a patient were to develop infection after an injection. The boiling of syringes is a troublesome procedure, but a doctor who employed only all-glass syringes and who sterilized them by boiling, would be legally unassailable and, what is perhaps equally important, ethically unassailable too.

FIG. 1.—Sterilizer

Much trouble and frequent renewals will be saved if all steel instruments are carefully dried after use, and some machine oil is dropped into the hinges before they are put away.

SUTURES, SUTURE MATERIALS AND LIGATURES

Suture materials today are obtainable in attractive and convenient form. Plastic sutures (fine suturing gut with cutting needle attached), made up each in its own glass ampoule with needle attached (fig 3b), are reliable and

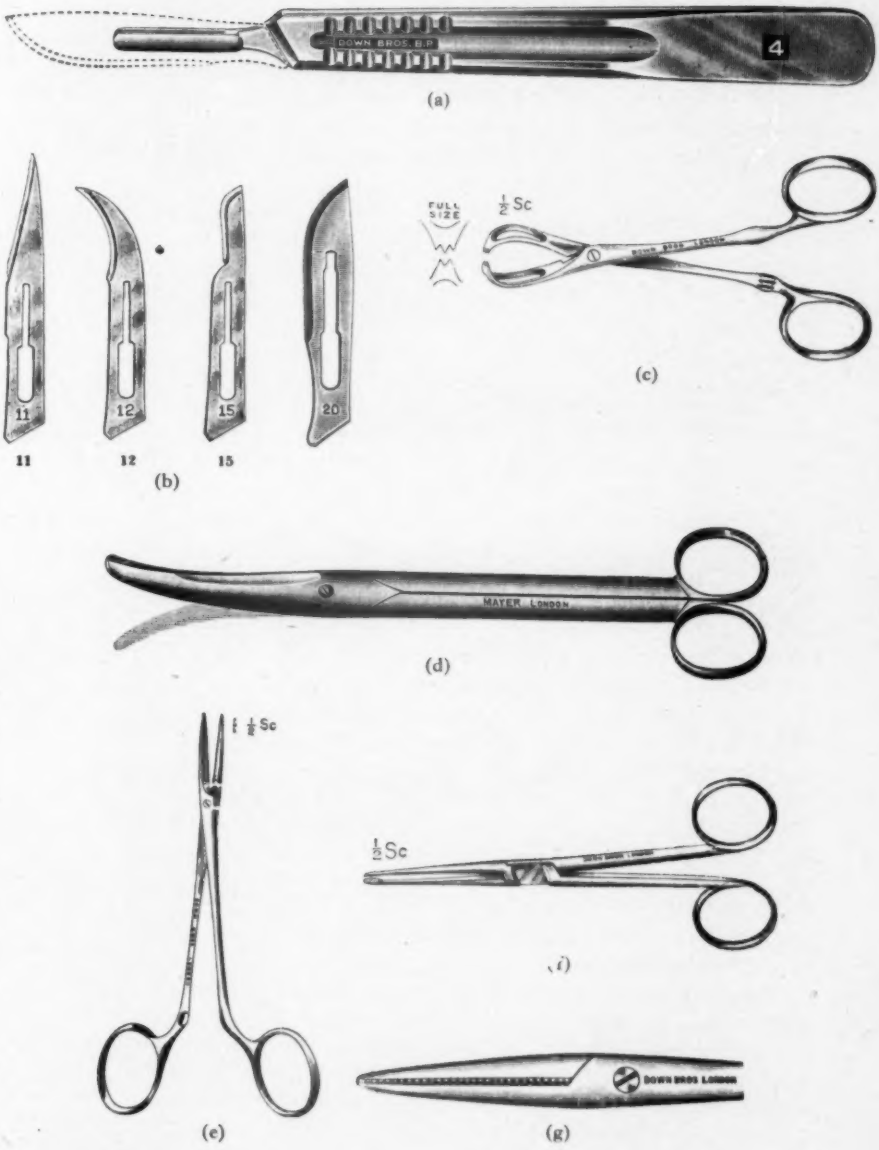

FIG. 2.—(a) Scalpel handle for large blades. (b) Scalpel blades, no. 11, 12, 15, 20. (c) Lane's tissue forceps. (d) Mayo curved scissors. (e) Halstead's 'mosquito' forceps. (f) Lister's sinus forceps. (g) Spencer Wells' artery forceps.

reasonably cheap. Catgut, for ligatures and sutures in deeper layers, should always be bought in sterile ampoules, rather than dry for subsequent sterilization. For general use the non-boilable ampoules are best.

Many practitioners prefer to buy their own needles and suture materials for closing the skin. The choice of needles is largely a personal matter, but for skin suture a cutting point is essential. A long needle (which need not

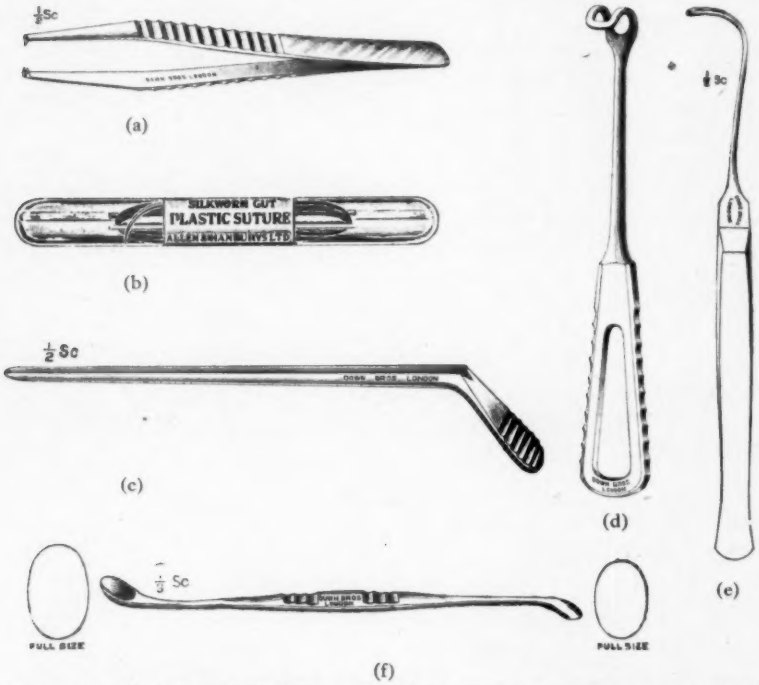

FIG. 3.—(a) Treve's dissecting forceps. (b) Plastic suture in glass ampoule. (c) Guy's grooved director. (d) Retractor. (e) Syme's aneurysm needle. (f) Stanley Boyd's scraper.

necessarily be a coarse needle) is suitable for hand stitching; a small needle requires a needle holder.

Whether gloves are worn for suturing a wound will depend to some extent upon the taste of the individual doctor, but many family doctors now like to use the service of sealed sterilized glove drums which many instrument makers have established. The use of gloves is essential if the wound may be contaminated with virulent organisms. If gloves are worn, a needle holder is almost essential.

For suturing the skin monofilament material, such as silkworm gut or nylon, or non-mesh serum proof woven materials such as impregnated silk or linen, should be used. Silk and linen are pleasanter to work with, knot more easily, and give neater apposition.

For ligatures to arrest hæmorrhage catgut is usually employed, but fine silk or linen thread, sizes 60 or 90, can be used safely in clean wounds. They can be sterilized by boiling, they are very much finer than catgut of equal strength, and they produce no foreign-protein reaction.

Accurate suturing demands a good light. A battery-operated head lamp, carried in the accident bag, will often prevent a surgical operation degenerating into groping guess-work.

HÆMORRHAGE

When called to a violent hæmorrhage, the medical attendant is wise always to avoid the old-fashioned tourniquet, which has lost more limbs than it has saved lives. When a doctor is called to a serious hæmorrhage, usually his first action is to replace the tourniquet that the first-aid worker has applied by his sphygmomanometer band. The sphygmomanometer is often a most valuable machine at the scene of an injury. It should be a surgical rule that no patient is sent off in an ambulance with bleeding controlled by constriction of the whole limb. Hæmorrhage that cannot be controlled by pressure of a dressing, demands that the first doctor to see the patient should apply an artery forceps. So that this may be done, the sterilizer in the accident bag should contain two or three rather larger artery forceps of the Mayo pattern. Immediate ligation at the place where the actual injury occurred is the best treatment for hæmorrhage from one of the larger vessels.

ANÆSTHESIA

For minor surgery the doctor must often be his own anæsthetist. Anæsthesia by freezing is suitable only for the opening of subcutaneous abscesses, and it is effective only if the skin is frozen hard. Ethyl chloride should be sprayed over an area the size of half-a-crown, that includes the site of the proposed incision, and spraying should be continued until the skin blanches and sounds like wood when struck with the handle of the knife. It is like wood and the knife must be pointed and sharp to penetrate it.

For the removal of lipomas or cysts, or the suture of small wounds, the best local anæsthetic is 0.5 per cent lignocaine ('xylocaine'), to which one drop of adrenaline solution should be added to each 10 ml. The anæsthetic should be injected at least an inch outside the area of operation, and at least eight minutes before it is due to start. Local anæsthesia requires a fine 3-inch needle of the Labat type that will fit the syringe to be used.

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REVISION CORNER

NYSTAGMUS

THE word nystagmus is from the Greek and literally means nodding, but in its accepted sense it stands for regular involuntary oscillation of the eyes. The oscillatory movements may be in a horizontal or a vertical plane or, more rarely, may have a rotatory quality. With mild degrees of nystagmus, the movement is absent when the eyes are in the position of rest, and deviation of the gaze away from the midline is needed to bring it out, lateral fixation being more likely to provoke it than looking up or down. In more severe grades, it accompanies deviation of the eyes equally in every direction, and may also be present in the midposition. It is termed *fine* if the range of oscillatory travel is small, and *coarse* if the latter is large: and it is a usual corollary that fine nystagmus is rapid, whilst coarse nystagmus is by comparison slow.

In its common form nystagmus has two phases, a slow drift of the eyes away from the direction of voluntary fixation, followed by a faster jerk back again. Sometimes, however, the two phases are at the same rate, and when this is so the resultant nystagmus is spoken of as *pendular*. If the pendular movements are of small excursion, so that the eyes show a fine shivering which may escape notice until ophthalmoscopic examination of the fundus is attempted, it is often called *jelly nystagmus*. Occasionally nystagmus is restricted to, or is much more obvious in, one eye than the other, and this type is known as *monocular* (*or ataxic*).

In physiological terminology, the designation of nystagmus as being to right, left, up or down, indicates the direction of the quick phase of nystagmic oscillation. This strict usage has no place in clinical practice, where the label of nystagmus in a certain direction simply means that involuntary movements appear when the eyes are turned in that direction, and their exact pattern can be further qualified descriptively if need be.

THE SIGNIFICANCE OF NYSTAGMUS

Nystagmus is, of course, one of the most familiar hallmarks of neurological disease and, although it usually implies such, it can have other causes, for it may be the result of visual defect, or an expression of labyrinthine disorder; in certain circumstances it also appears as a normal physiological response.

PHYSIOLOGICAL NYSTAGMUS

There are two well-known purely physiological forms. One is *optokinetic nystagmus* which is called forth by looking at a moving scene; for example, from a railway carriage window. The eyes fix on some outside object, and track with it until it is cut off from view, when they quickly jerk back to pick up some new point of interest, to repeat the same process over and

over. The locking-on of the gaze which leads to the phenomenon seems to happen at a reflex level, for it requires deliberate effort to prevent it. The other is *labyrinthine nystagmus*, which results reflexly from stimulation of the semicircular canals. It can be induced either by rotating a normal subject in a revolving chair for about half a minute, or by irrigation of the external auditory meatus with hot or cold water. The latter method forms the basis of the Bárány caloric tests used to assess labyrinthine function, which are of great value in the diagnosis of such conditions as Ménière's syndrome and auditory nerve tumour.

OCULAR NYSTAGMUS

Nystagmus of pendular type, often slow and rather irregular with a quasi-searching appearance, is not uncommon in children or adults blind from birth as a result of corneal or lenticular opacities or retinal dysplasia. It may also rarely be met as a truly congenital trait, with distinct familial inheritance, unaccompanied by gross fault in the eyes beyond a refractive error causing myopia or astigmatism. A visual type of nystagmus can happen as an occupational hazard: in this country it is largely an affection of miners. It used to be thought that years of exposure to poor light at the coalface caused it by gradually establishing automatic oscillations to make use of the extra-macular retina, but the tendency now is to regard it as a habit spasm in which psychoneurosis plays a large part.

LABYRINTHINE NYSTAGMUS

In recurrent aural vertigo (Ménière's syndrome), which is chiefly an affection of late middle life, nystagmus is always well marked if the patient is seen during an acute attack. It can sometimes also be demonstrated in the free intervals, particularly if the eyes are examined with the head in different positions. The mechanism of the vertiginous episodes is still not fully understood, but it seems likely that fluctuations in endolymph pressure in the diseased labyrinth is the fundamental factor. Similar severe vertigo and loss of balance, with nystagmus, are also encountered when suppuration spreads to the labyrinth from infection in the middle-ear cavity.

NYSTAGMUS OF NERVOUS ORIGIN

When disease of the nervous system leads to nystagmus, it is often assumed to be (of necessity) a sign of cerebellar dysfunction. It is indeed the case that most cerebellar lesions in man, except those which are restricted to the vermis, present it as a prominent feature, but clinical experience and physiological experiment both underline that damage to the brain-stem in the neighbourhood of the vestibular nuclei is an equally, or even more, potent cause for its appearance. In effect, nystagmus implies disturbance of the neural mechanism which controls movement and posture of the eyeballs, and such injury may take place at any one of three points: in the

cerebellar hemisphere, from brain-stem mischief impinging directly on the vestibular nuclei in the pons, or at ponto-mesencephalic level from interference with the posterior longitudinal bundle and other associated tracts which carry vestibular and cerebellar outflow to the nuclei of the external ocular muscles.

CEREBELLAR NYSTAGMUS

The nystagmus which results from lesions of the cerebellar hemispheres can be regarded as an incoordination of eye movements strictly comparable to the incoordination which cerebellar deficit imposes on control of the limbs. Although it is not purely ipsilateral, as is the limb ataxia with unilateral disease, it is always slower and coarser on looking towards the affected side than on looking away. It is rhythmic in character, and at first appears only in lateral gaze, although as the causal lesion progresses it also becomes apparent looking up and down. It may be due to intrinsic tumour of the glioma series (astrocytoma or hæmangioblastoma) or to metastasis, or may be secondary to compression of the cerebellum by extrinsic tumour, such as acoustic neurofibroma (which is the commonest posterior fossa neoplasm of adult life) or meningioma. A cerebellar abscess secondary to middle-ear infection is not infrequent, particularly in childhood, and occasionally a solitary cerebellar tuberculoma presenting with a tumour syndrome may be met, again chiefly in childhood. The various forms of atrophy of the cerebellum usually only cause nystagmus at a late stage in their evolution, long after other signs of cerebellar deficiency have become manifest. The superior cerebellar artery is responsible for a large part of the blood supply of the hemisphere, and is occasionally blocked by a thrombus or embolus, which results in nystagmus with an ipsilateral cerebellar syndrome, and crossed spinothalamic sensory loss from associated lateral brain-stem infarction.

BRAIN-STEM NYSTAGMUS

From a statistical point of view, there is no doubt that nystagmus arises far more often from brain-stem damage than from cerebellar disorder, for there are both more numerous and more frequently occurring pathological processes which may interfere with relevant nuclear or nerve fibre systems here.

Disseminated sclerosis, the commonest of all nervous diseases, is a prime cause because its plaques have nearly as strong a tendency to occur in the brain-stem as in the spinal cord, and nystagmus at some stage of its course is almost invariable. The pattern of nystagmus is very variable. It may simply be of the usual kind, but rotatory components may be present, there may be jelly nystagmus, or nystagmus may develop much more positively in the abducting eye than in the eye which moves to the inner canthus when the gaze is turned laterally to either side. This kind of monocular

nystagmus is rare except in disseminated sclerosis, as is jelly nystagmus too, although neither is strictly pathognomonic.

Vascular lesions of several kinds may induce nystagmus. In the last dozen years or more, the occurrence of *angiomas* in the central nervous system has increasingly attracted the attention of neurologists. These blood-vessel malformations are of congenital origin, and are not neoplasms although they may gradually enlarge over the years. They cause symptoms chiefly by rupture with hæmorrhage into adjacent nervous tissue or sub-arachnoid space, or by thrombosing. The brain-stem seems to be a relatively favoured site for small capillary angiomas, which are capable of causing nystagmus, along with other signs. If there is remission and relapse (as there may be), then a false diagnosis of disseminated sclerosis is likely to be made, which is only corrected at necropsy. *Thrombosis* of nutrient vessels to the brain-stem, of which the syndrome of the posterior inferior cerebellar artery is the best known, may be another cause of nystagmus, but stenosis or occlusion of the basilar artery itself, or basilar aneurysm, can occasionally be responsible as well. *Gliomas* sometimes occur in the brain-stem, more often in childhood than in adult life, and nystagmus may then be a sign of their presence, usually along with cranial nerve paralyses and indications of long tract motor and sensory dysfunction.

Infections may be a cause. Poliomyelitis in its bulbar form can lead to tremulous nystagmus-like movements of the eyes, which have been given the name of opsoclonus. Virus encephalitis of several forms, including von Economo's, is apt to show a predilection for attack on brain-stem structures, and involuntary movements of the eyes, often suggesting a kind of ocular tremor rather than a frank nystagmus, may be seen, although the latter is also possible. True nystagmus is a characteristic of the syndrome of epidemic vertigo, several accounts of which have been published in recent years. There is severe vertigo with loss of balance, and nausea or vomiting, plus malaise and sometimes mild fever, all of acute onset and subsiding usually in a week or less. Although it has been regarded by some as due to acute labyrinthitis, there are reasons for suspecting that it may be an affection of nerve cells in the vestibular nuclei: i.e. a neuronitis rather than a semicircular canal affair.

Head injury can also cause nystagmus, which is usually of brain-stem origin (although in wartime penetrating cerebellar wounds of course produce it). It is uncommon and is a sequel only of very severe concussion, with prolonged post-traumatic amnesia. Its appearance may be associated with other signs of stem contusion, which may include Parkinsonian features.

Brain-stem nystagmus is a prominent sign in *metabolic disorders* of the type of Wernicke's encephalopathy, where the primary etiological factor is aneurine deficiency. The latter may be the result of simple starvation, but commonly is a symptom of chronic alcoholism, carcinoma of the stomach,

or defective intestinal absorption from steatorrhœa. Along with nystagmus there are mental confusion, pupillary anomalies, defects of conjugate ocular movement (particularly of upward and downward gaze), and signs of peripheral neuropathy may also be present.

MISCELLANEOUS CAUSES OF NYSTAGMUS

Paretic nystagmus.—Very rarely nystagmic jerking may be observed with external ocular muscle paresis. It develops when the eye is turned by the weakened muscle (or muscles), and is simply an expression of weakness.

Pseudo-nystagmus.—In some normal subjects involuntary movements of the eyes occur at the extremes of lateral ocular deviation. These can be distinguished from real nystagmus by their irregularity of rate, for it is one of the characteristics of the latter that it is plainly rhythmical, even when it is non-persistent.

Drug nystagmus.—The barbiturates are capable of inducing disorders of gait and balance with well-marked nystagmus even in small doses in some people who are unusually sensitive to them. Intoxication can sometimes be mistaken for cerebellar tumour or other serious disease, if it occurs in a secret drug addict, particularly if there is complaint of headache (really of neurotic origin) at the same time.

DISCUSSION

Two final comments are called for. First, with regard to symptoms from nystagmus. It is usually subjectively silent, but now and then intelligent patients will say spontaneously that objects seem to jump when looked at from the corner of their eyes, whilst others simply state that fixation at the extremes of gaze produces an uncomfortable feeling. Secondly, about examination for nystagmus. The patient should be asked to watch the examiner's finger or some other convenient article, like a pen or tendon hammer handle. The test object should be at a range of two to three feet, not closer, as it may then be impossible for the patient to focus it properly, with resultant lack of cooperation. It should be moved sideways until the extreme of lateral conjugate deviation is obtained, and it is important not to be hasty, for unless the patient's eyes are maintained in steady lateral gaze for some seconds, nystagmus may be missed. After examination to either side, upward and downward gaze can be tested. If nystagmus is not clear-cut, but is suspected of being present, it can be helpful to make the patient look quickly from side to side several times before finally fixing his gaze, as it may be potentiated by this manœuvre. It is also worth while examining for nystagmus with the head both supine and erect, as it may be more obvious in one position than the other, particularly if it is labyrinthine in type.

MICHAEL JEFFERSON, D.M., M.R.C.P.
Consultant Neurologist, Queen Elizabeth Hospital, Birmingham.

NOTES AND QUERIES

Anticoagulant Treatment in Cerebral Thrombosis

QUERY.—I should be grateful for information on the use of anticoagulants in the treatment of cerebral thrombosis. Is there any definite indication for their use soon after the accident? If so, this raises the difficult question of making a definite diagnosis at this early stage. I should be grateful for any guidance in this matter.

REPLY.—It is obvious that anticoagulants should not be given if there is risk of hæmorrhage. In a case of sudden hemiplegia the clinical distinction between hæmorrhage and infarction is often difficult. Moreover, if the cause be infarction the infarct may be hæmorrhagic. This is especially likely to be the case if the arterial occlusion is embolic, and pathological investigation suggests that when atherosclerosis is present in one of the larger vessels—for example, the internal carotid—detached thrombus from this site may often be the cause of a peripheral occlusion, rather than primary thrombosis in the peripheral branch. These are the arguments that prevail with many physicians against the use of anticoagulants immediately after the accident in a case of hemiplegia.

If after the initial ictus there is brief improvement with relapse and extension of paralysis, without symptoms of increased intracranial pressure, there is probably a spreading thrombosis. This is the best indication for the administration of anticoagulants. If there is doubt in such a case between the diagnosis of cerebral hæmorrhage and cerebral infarction, lumbar puncture should be done, provided there are *no* symptoms of increased intracranial pressure, and that a few ml. only of fluid are withdrawn. If the cerebrospinal fluid is bloodstained anticoagulants should not be given.

SIR CHARLES SYMONDS, K.B.E., C.B., M.D., F.R.C.P.

Recurrent 'Sore Throats'

QUERY.—A woman, aged 56, has had five attacks of sore throat, the first in 1935, the next at the end of the War and three attacks in the last three years. She is not subject to colds or coughs, and the pattern of the sore throats has been the same each time. She wakes feeling the soft palate stiff and sore. During the first day, and only on the first day, a plug of pink mucus is hawked from the nasopharynx. The temperature for the first few days varies from 99° to 102° F. (37.3° to 39° C.), and the pulse (normally 60 to 72) is 72 to 84 and she sleeps more or less all day and night. The soreness flits from one pillar of the fauces to the other for about a week but the tonsils do not enlarge. There is then a spread downwards and on four occasions there has been a pneumonitis; on only one occasion was the chest x-rayed and then pleural thickening and adhesion at the left base were seen. An x-ray a month later was clear. At the end of the second week of illness there is sudden anorexia and, on three occasions, repeated vomiting for a day. Thereafter, she gradually recovers, feeling very weak for at least six weeks.

I should be most grateful for comments and advice.

REPLY.—This interesting case report raises several points, of which the following would seem to be the most important.

As five attacks of sore throat have occurred in the last three years, the possibility of a septic focus in the upper respiratory tract obviously arises. This lady should have a full examination of her nose and throat. Although the tonsils do not enlarge during her attacks, they may well be infected. The recurrent upper respiratory infections may be a manifestation of a general disease and a full blood count should be done.

Each infection seems to be a pretty formidable affair, consisting of a sore throat with fever for a week, then a pneumonitis, then lassitude for six weeks. One such attack might well be accounted for by a virus pneumonia, but this diagnosis hardly accounts for so many attacks. The evidence of pneumonitis, in the absence of x-rays of the chest, is questionable. If the pneumonitis always occurs in the same place, then there may be a local disease, such as bronchiectasis. This could be determined by bronchography. If any precipitating cause of the attacks can be found, perhaps the early administration of a suitable antibiotic would shorten the duration of disablement. The choice of antibiotic would depend to some extent upon the organisms found in throat swabs and sputum.

NEVILLE OSWALD, M.D., F.R.C.P.

Recurrent Herpes

QUERY.—I have a patient with a recurrent herpes of the left side of the face. This has occurred every three to four weeks for the past eighteen months. I have referred her to two local dermatologists and she has had the following treatment with no effect: 'Cytamen'; intramuscular injections of iron; x-rays; vaccination; 'chloromycetin'; surgical spirit; antibiotic creams; antihistamines; and 'achromycin'. Could you please suggest any further possible lines of treatment?

REPLY.—The multiplicity of remedies tried in-

dicates the uncertainty of therapy in recurrent herpes. In my experience the only treatment which has given any consistent results has been x-rays; if this patient has only received a small dose I would suggest repeating this, giving three doses of 125r (unfiltered) at 70 kv. at three-weekly intervals. At the same time she should be carefully investigated for any focus of irritation in the fifth nerve area, such as an unerupted tooth or an apical abscess, which should be treated. In the absence of this I would suggest the old-fashioned remedy of Fowler's solution (arsenical solution B.P.), starting with 1 minim (0.06 ml.) three times a day and increasing by 1 minim a day up to 5 minims (0.3 ml.) three times a day, and then decreasing again.

F. F. HELLIER, O.B.E., M.D., F.R.C.P.

Combined Immunization

QUERY.—I would be grateful for an opinion on the advisability of using combined prophylactics against diphtheria, pertussis and tetanus, starting at about the fourth month and preceded by smallpox vaccination at three months.

Are the present commercial preparations composed of optimum ratios of the three components, so that there is no excess of tetanus toxoid to suppress the response to the diphtheria toxoid, and are the triple vaccines now to be preferred to separate injections of the three antigens?

If the child has already received two injections of diphtheria toxoid is it permissible to give the first dose of whooping-cough prophylactic with the third diphtheria injection without fear of suppressing antigenic response?

When planning booster doses is it advisable to give a boosting injection of pertussis at about the first birthday and then employ diphtheria-tetanus prophylactic for boosting at 5 years and 9 to 10 years, or is it better to include whooping-cough prophylactic at five years?

REPLY.—There is a great deal to be said for using triple antigen for routine immunization against pertussis, diphtheria and tetanus and satisfactory commercial preparations are available. It must be remembered, however, that the protection against pertussis is less well maintained than that against diphtheria and tetanus and should therefore be boosted at yearly intervals (or after any known contact with a child suffering from whooping-cough).

As whooping-cough is most dangerous in early infancy it would be wiser to start with a triple antigen at the age of one month, repeat it at two months and three months and proceed to smallpox vaccination at four months.

In the case of an infant who has already had two injections of diphtheria toxoid the first pertussis vaccine should certainly be given alone because suppression of pertussis antigenic response may well occur if a combined prophylactic is used. With regard to booster doses it would be better to repeat the tetanus toxoid at two years instead of waiting until five years.

Pertussis immunization is not usually considered necessary after five years of age.

PROFESSOR WILFRID GAISFORD, M.D., M.SC., F.R.C.P.

Children in West Africa

QUERY.—In a few weeks, one of my patients (qualified but non-practising at present) is flying to Nigeria with her two small children. They will be living in the forest belt, without easy access to medical supplies, for a period of about eighteen months. Can you please suggest a 'short list' of preparations which it would be advisable for her to take to cover possible contingencies—from prickly heat to snake bite as well as common ailments!—bearing in mind the limitations imposed by air travel and storage under tropical conditions? Are the majority of drugs we know available in Lagos and is there likely to be any difficulty with the customs?

I should be grateful for any general advice to pass on, in particular the antimalarial and T.A.B. dosage recommended for children—aged 12 months and 2½ years. The elder boy suffers from flexural eczema. Would this warrant any extra precautions?

REPLY.—The commonest conditions liable to be contracted in Nigeria are malaria, dysentery or gastroenteritis, and short-term fevers probably caused by viruses. Supplies of an effective antimalarial substance should therefore be taken and of these proguanil is as reliable as any and at the same time the least toxic. Sulphaguanidine or phthalylsulphathiazole are the most satisfactory drugs for general use in dysentery and infective gastroenteritis. For symptomatic treatment of short-term fevers a supply of aspirin or compound codeine tablets should be taken.

For travel sickness either hyoscine or 'avomine' is satisfactory in the majority of cases. There is no effective prophylaxis for prickly heat in those especially susceptible but the wearing of suitable clothing and frequent bathing will prevent its development in many instances.

Snake bite is much less common than most travellers fear and it is more than probable that antivenine, no matter how often procured for an ordinary household, will reach its expiry date unused. Messrs. Allen and Hanburys, however, stock serum for the African snakes under the code letters A.N. The dose is 10 to 20 ml. and the serum remains active for five years.

To the drugs here mentioned, those required

for simple cuts and abrasions should be added.

There are excellent pharmaceutical facilities in Lagos and almost all drugs are procurable there. There is unlikely to be any difficulty with customs in connexion with small quantities of non-dangerous drugs which are to be taken into Nigeria for personal use only.

In tropical Africa it is recommended that for malaria prophylaxis 50 mg. proguanil be given daily to the children aged 12 months and 2½ years and that this be increased to 100 mg. daily at the age of 7 years. Alternatively, pyrimethamine, 12 mg., or chloroquine, 150 mg. (base), may be administered weekly.

The recommended dosage of T.A.B. for a child aged 12 months is 0.25 ml. followed in one week by the same amount of a suspension containing 1000 million *B. typhosum* and 500 million *B. paratyphosum* A and B. For the child aged 2½ the second dose could be increased to 0.5 ml.

It is not possible to say whether tropical residence and all that it entails is likely to aggravate or relieve the flexural eczema from which the elder child suffers. In general, those with skin diseases do not do well in the tropics but there is no hard and fast rule concerning this.

PROFESSOR A. W. WOODRUFF, M.D., PH.D., F.R.C.P.

Prolonged Iron Therapy

QUERY.—I should be grateful for advice on the matter of prolonged administration of oral iron —with particular reference to female patients at the menopause. I have heard it said that the long-continued administration of iron tends to mask the deterioration in the blood-forming organs—with a sudden collapse in their function. Also that prolonged iron therapy tends to 'bowel changes'. I would be glad to know the modern ideas on this subject and what bowel changes do actually occur. Also for how long is it safe to give iron?

REPLY.—There is no authentic evidence that long-continued administration of oral iron in therapeutic doses will mask deterioration in the blood-forming organs. Such deterioration is not an accompaniment of the menopause. Oral iron in therapeutic dosage does not cause toxic intestinal changes, nor does it lead to sudden failure of the hæmopoietic system. If oral iron is taken in a massive overdose, then acute gastro-intestinal damage, amongst other effects, may occur. Fatal cases have been reported, but these have been almost invariably children who have mistaken the iron tablets for sweets. If a child recovers from the acute effects of such excessive overdose, a secondary fibrosis may lead to stricture of the gut, e.g. pyloric stenosis.

Oral iron can be given indefinitely in therapeutic doses, because a special intestinal barrier mechanism regulates its absorption according to the needs of the body. The latter should be assessed by a blood examination before treatment is begun and also during treatment for, whilst the commonest primary anæmia at the menopause is of iron-deficiency type, other anæmias including pernicious anæmia occur sufficiently often at the same age to make this worth while. If, however, facilities for blood examination are not available and, after careful clinical examination, there is evidence of nothing other than simple iron deficiency, then oral iron may be given in therapeutic doses for a trial period of two months. If there is no satisfactory clinical improvement by that time a full clinical investigation should be made to search for an underlying cause such as carcinoma, and for this the patient may have to be referred to hospital.

E. K. BLACKBURN, M.D., F.R.F.P.S.

Pyospermia and Infertility

QUERY.—I have a case of infertility in which the wife has undergone the customary full investigation and may be considered potentially fertile. The semen investigation of the husband normally gives a very satisfactory result as regards sperm count, which is in the order of 196,000,000 per ml., of which some 75% are motile and there are no abnormal forms present. Each sample, however, shows the presence of polymorphs to the extent of 1 million per ml. Gram-staining of the film does not reveal the presence of bacteria.

I referred the husband to a local consultant-surgeon, who is especially interested in genito-urinary disease. The results of his investigations were for the most part negative but a prostatic smear showed occasional polymorphs and gave a profuse growth of *E. coli* on culture. His opinion was that the patient, who had suffered a good deal from dysentery while abroad, had a chronic prostatitis and that little could be done apart from attempting to treat the infection by general measures including antibiotics. I should be grateful to know if this intrusion of polymorphs is a well-recognized condition and if it is considered to be a bar, or at least a hindrance, to conception. Also, if you think it would be worth while advising the husband to attend a specialized clinic or consultant for further help.

REPLY.—It is common to find polymorphs in semen, and I should regard 1 to 2 million per ml. as a 'normal' finding. By itself even an excess of these cells, i.e. a true pyospermia, does not affect the fertilizing capacity of semen, although it does indicate an infection in the urogenital tract

and should be investigated for the sake of the patient's general health.

In this particular case I should not consider any further investigation and treatment of the husband; if there is no doubt as to the adequate density, motility and morphology of his spermatozoa then the couple's failure must be due either to some gynæcological abnormality or to inefficient coitus.

H. A. DAVIDSON, M.R.C.S., L.R.C.P.

Aviation Œdema

QUERY.—I have a middle-aged female patient who complains that when she flies she gets what appears to be a form of angioneurotic œdema, in that her hands and feet swell to the extent that she has to take off her rings and shoes. This persists for some three hours after landing.

Can you suggest any treatment?

REPLY.—Postural œdema is a condition of relatively common occurrence in flying, the incidence of which varies according to the length of flight, the age of the passenger, and any deficiency in the cardiovascular system. There is very little trouble on short flights of two to four hours and most cases are reported on long flights involving many hours or days.

Postural œdema is a condition in which the body fluids collect in the dependent parts of the body. This is brought about by the following factors:—

(a) Prolonged retention of the feet and ankles in the dependent position.

(b) Pressure by angular edges of seats on the veins and lymphatic vessels at the back of the legs.

(c) Absence during flight of muscular contractions in the muscles of the lower limbs present in walking or other forms of exercise.

(d) The fine, high - frequency vibrations present in aircraft in flight.

These factors lead to a diminished return of fluids to the heart and a pooling in the most dependent parts of the body such as the legs, feet and ankles. The condition is aggravated in any passenger who has a weak heart, and is more common in persons over 50 years of age.

Prevention is simple and consists of ensuring that the feet can be elevated to a height equal to that of the pelvis. Return of blood and other body fluids to the heart is thus facilitated and the condition will not occur. Such conditions can be assisted by the provision of seats in which pressure on the popliteal area is avoided and which can be adjusted to the fully reclining position with the feet elevated, or some form of leg-rest which will achieve the same result as above. Alternatively the provision of bunks will prevent the onset of the condition by allowing the passenger to rest in the fully recumbent position for periods during the flight.

So far as the swelling in the hands is concerned, this might well be due to a similar condition due to letting her hands hang down, or to the lymphatic and venous return being impeded by her upper limbs hanging over the arms of the seat.

KENNETH BERGIN, M.D., D.P.H.

PRACTICAL NOTES

Migraine in Children

WRITING from the Mayo Clinic, E. C. Burke and G. A. Peters (*American Journal of Diseases of Children*, October 1956, **92**, 330) report on their findings in a group of 92 children with migraine. The sex ratio, 63 boys and 29 girls (i.e. more than 2:1) was quite different from that in adults, of whom 65% to 75% are women. The age at onset ranged from 1½ to 14 years, with an average of 7.3 years: approximately 17% were less than 5 years at the time of onset. Electroencephalograms were recorded in 67 cases, and 46 were abnormal, compared with an incidence of 15% to 20% of the normal child population. Frontal and orbital headaches were described by 63 children. The most distressing symptoms were nausea and vomiting, which were present in 74 children. Only nine children had scotomas. A family history of migraine was obtained in 40 cases. A history of allergy was only elicited in 11 cases. No significant correlation was present between the allergic symptoms and attacks of migraine. In 26 children attacks were precipitated by emotional factors. The frequency of attacks ranged from attacks nearly every day to one every month or so. A follow-up failed to reveal any evidence that children who have migraine cease to be affected as they reach adulthood. For treatment the best agent is considered to be aspirin 'if it can be administered in a sizeable dose (1 grain [65 mg.] per year of age when given orally or 2 grains [0.12 g.] per year when given rectally) early in the attack'. A combination of ergotamine tartrate and caffeine ('cafergot') is less effective than in adults. It is also suggested that a trial of anticonvulsant drugs in adequate doses may be a useful prophylactic measure.

'Normal' Blood Pressure

A NEW scale of average blood pressures and normal ranges at different ages is put forward by H. Temple Phillips (*Medical Officer*, November 9, 1956, **96**, 285) on the basis of his findings in 3,233 persons (1,583 males and 1,650 females),

Age group	MALES	
	Average	Range
15-19	126/74	108/56-143/93
20-24	127/77	108/59-145/94
25-29	128/79	109/62-147/95
30-34	130/81	110/64-150/96
35-39	132/82	111/66-153/97
40-44	134/83	112/67-157/98
45-49	137/84	114/68-163/99
50-54	142/85	116/69-169/100
55-59	147/86	119/70-176/102
60-64	153/87	123/71-184/105

between the ages of 15 and 64 years, who were examined in connexion with their employment by the Bristol Corporation. The great majority of the blood-pressure readings were taken with the candidates in the sitting position. The

Age group	FEMALES	
	Average	Range
15-19	121/75	101/58-138/92
20-24	121/76	102/59-140/93
25-29	122/77	103/61-143/94
30-34	125/79	104/63-147/95
35-39	129/81	105/66-152/96
40-44	133/83	108/68-157/97
45-49	137/85	112/69-162/99
50-54	142/87	116/71-168/102
55-59	147/89	120/72-174/105
60-64	153/91	125/72-180/108

accompanying tables show the author's proposed new scale of 'normal' pressures for men and for women.

Recording the Blood Pressure in the Obese

'IN markedly obese individuals, the true arterial blood pressure may be more accurately determined by measuring blood pressure in the forearm rather than in the upper arm', according to K. W. Trout *et al.* (*Journal of the American Medical Association*, November 3, 1956, **162**, 970). This is done by placing the standard 13-cm. cuff on the forearm with its midpoint 13 cm. from the olecranon process, and the blood pressure is determined by either auscultating or palpating the radial artery. In a series of 100 subjects, in whom the reading obtained by this method was compared with the reading obtained by the more usual method of using the upper arm, the difference was 10 mm. Hg or less in 79. There was a difference of 10 to 20 mm. in 17, whilst in four it exceeded 20 mm. Hg. All these last four were obese subjects. In a further 14 subjects the blood pressure obtained by these two methods was compared with the intra-arterial brachial pressure. In eight of these there was no significant difference between the three readings. In the remaining six subjects, who were all obese, the upper arm reading was significantly higher than the forearm reading, and in all of these the intra-arterial pressure correlated closely with the latter.

Chlorhexidine in Urology

CHLORHEXIDINE ('hibitane') 'is of great value as a urological disinfectant', according to H. Beeuwkes and H. R. de Vries (*Lancet*, November 3, 1956, **ii**, 913). Its value in this field lies in the fact that it is active against *Ps. pyocyanea*. Beeuwkes and de Vries report on the use of chlorhexidine in conjunction with cystoscopy. The rinsing fluid for the irrigator consisted of a 1:10,000 solution of chlorhexidine (1 g. in 10 litres of tap-water at 40° C.). For bladder irrigation and as the cystoscopy medium the concentration was 1:5000 ,and for disinfection of the external genitalia it was 1:1000. The tap of the irrigating tube and the sliding switch for the light were immersed between cystoscopies in a 1% solution of chlorhexidine in 70% alcohol. The hands of the staff were rubbed several times a day with a cream comparable to 'hibitane antiseptic cream', which contains 1% chlorhexidine in a water-miscible cream base. In the 50 consecutive cases examined by cystoscopy before the introduction of this technique, 70% of the urine samples became infected: 56% *Ps. pyocyanea*; 10% *Proteus;* 4% *Staph. albus*. In the next 50 patients, in whom the chlorhexidine technique was used, the infection rate was only 8%, all infected with *Staph. albus*.

Infectious Reticulo-Endotheliosis

'AN apparently specific virus disease involving the reticulo-endothelium and related cells of the body' is reported by L. F. Koyl (*Canadian Medical Association Journal*, November 1, 1956, **75**, 709). The report is based upon the findings in 205 cases seen between July 1952 and November 1955. These consisted of nine children under the age of 12 years, and 196 adults (136 women and 60 men). The disease is defined as 'a prolonged illness characterized by profound asthenia, irritability, anorexia, nausea, generalized aches and pains, a dry, irritating nonproductive cough, bouts of spastic intestinal pain, and in females, disturbed menses'. The characteristic sign is lymphoid hyperplasia, most evident as enlarged glands in the neck (193 patients), but these were also often present in the groin (122 patients) and the axillæ (112 patients). The spleen was palpable in 82 patients, and the liver in 40. The appearance of the naso-

pharynx was almost diagnostic. There was no erythema, but 'each lymph follicle stood out clear, glistening and swollen to hemispherical shape'. The blood smears presented a typical picture. In patients seen during the first week there was often leucopenia and 'toxic granulation of leucocytes'. Later there was a lymphocytosis. In 50 cases there were more mononuclears than neutrophils in the blood smear. During periods of activity of the disease the characteristic cell was the reticulo-endothelial cell, or monocyte. Later in the disease the dominant cell became an abnormal lymphocyte with 'water-clear blue cytoplasm'. A positive urobilinuria was a common finding. The course of the disease was prolonged, ranging from 2½ months to an extreme of over two years in two patients. Treatment is symptomatic.

Prevention of Chlorpromazine Dermatitis

METHODS of preventing contact dermatitis when handling chlorpromazine hydrochloride ('largactil') are described by R. H. Seville (*British Journal of Dermatology*, October 1956, **68**, 332). Twelve members of the staff of a mental hospital who had been handling the drug developed contact dermatitis. In five cases, none of whom wore glasses, the onset was on the face, with 'redness, swelling and sometimes weeping of the skin, especially around the eyes, but also about the mouth', and in the other seven there was a rash in the clefts, or on the sides, of the fingers. When patch-tests were carried out all cases were positive to a 0.66% solution, and only two were negative to a 0.1% solution, of 'largactil' powder. Photosensitivity was found to be a contributory factor. In nine cases patch-tested with a fresh, 1% solution of another phenothiazole derivative, 'pacatal', results were positive in three, indicating cross-sensitivity between the two drugs.

The following precautions were taken to avoid contact with the drug: crushing or dissolving tablets, and the use of syrup or solution were forbidden; tablets were given with a clean spoon and the nurse was instructed to wash immediately afterwards (alternatively, the nurse wore rubber gloves); uncooperative patients received the drug by injection, the nurses wearing rubber gloves, masks and gowns, and avoiding droplet spray into the atmosphere by inserting the needle into a large piece of sterile cotton-wool when removing the air from the syringe. The fact that the greatest precautions are needed was shown by the patient who developed contact dermatitis after making beds in a ward where the drug was being given, and the pharmacist who relapsed after unpacking, but not opening, tablet containers (he was unaware of the diagnosis at the time). Since the original twelve cases, only four more of the nursing staff have developed chlorpromazine dermatitis, all of whom had ignored these precautions.

Pyrimethamine in Uveitis

BECAUSE of the evidence that toxoplasmosis is an etiological factor in at least a proportion of cases of uveitis, E. S. Perkins, C. H. Smith, and P. B. Schofield (*British Journal of Ophthalmology*, October 1956, **40**, 577) have investigated the value of pyrimethamine ('daraprim') in the treatment of 164 cases of uveitis. Pyrimethamine, originally introduced as an anti-malarial drug, has been shown to possess an antitoxoplasmic effect both experimentally and clinically. The dosage used in this investigation was one 25-mg. tablet daily. In addition, the patients received conventional medical treatment: e.g. mydriatics and cortisone. The results show that pyrimethamine 'exerted a statistically significant effect on the improvement of cases having a positive toxoplasma reaction'. It had no detectable effect on the improvement of cases with a negative toxoplasma reaction. The best response was obtained in cases of circumscribed choroidoretinitis. Attention is drawn to the toxic effect of pyrimethamine on hæmopoiesis. Of 113 patients in whom regular blood counts were performed, the hæmoglobin level dropped more than 5% in 53 (47%), 23 of whom showed macrocytosis in the film. In addition, three patients showed a slight fall in the leucocyte count. It is therefore recommended that regular blood counts should be performed while pyrimethamine is being administered.

Isoniazid and Cortisone in Rheumatoid Arthritis

ACCORDING to L. L. Wiesel (*American Journal of the Medical Sciences*, October 1956, **232**, 412), isoniazid 'strongly inhibits the inactivation of cortisone by liver slices'. He reports that under his experimental conditions between 88% and 89% of cortisone is inactivated with liver tissue slices. The addition of from 1 to 15 mg. of isoniazid, however, decreased inactivation to 18%. In view of these findings, with A. S. Barritt and C. J. Scheid (*Ibid.*, p. 415), he then proceeded to investigate the combined effect of isoniazid and cortisone in 39 patients with rheumatoid arthritis. These patients were given 37.5 mg. of cortisone acetate daily by mouth and 100 to 600 mg. of isoniazid daily. It is claimed that in these patients isoniazid 'definitely potentiated the anti-inflammatory effect of cortisone acetate since relapse during control periods was quite uniform irrespective of which of the two drugs were withdrawn'. It proved

possible to continue this treatment for periods exceeding one year in 24 patients, and for more than two years in nine patients. Treatment had to be stopped in one patient because of the development of paræsthesia. It is also claimed that this form of therapy was 'free of the side actions which occur with large doses of cortisone alone'. It is admitted that there is no satisfactory explanation of this last phenomenon, but it is suggested that 'smaller doses act in more physiologic fashion while larger doses produce a pharmacological effect with accompanying manifestations of an undesirable nature'.

Polyneuritis Due to Isoniazid

FIVE cases of polyneuritis in tuberculous patients receiving isoniazid are reported by G. Joly Dixon, G. B. S. Roberts and W. F. Tyrrell (*Scottish Medical Journal*, 1956, **i**, 350). In each case the polyneuritis developed while the patient was receiving isoniazid, and 'poisoning with isoniazid is suggested as the probable cause' of the polyneuritis. One of the patients, who had tuberculous meningitis, was receiving 18.7 mg. of isoniazid per kg. body weight, but the others were receiving less than 8 mg. per kg. body weight. In four of the cases the neuropathy cleared up spontaneously when isoniazid was withdrawn. In the fifth, an exacerbation of the neuropathy occurred soon after the dosage of isoniazid was increased, and in this case blindness and paraplegia developed, followed by a fatal termination. Necropsy revealed demyelination of the optic tracts and softening of the grey matter of the spinal cord.

Splenectomy in Hæmatology

OVER a period of seven years, splenectomy was performed in Belfast on 32 patients with hæmatological disorders. In an analysis of this series, M. G. Nelson (*Irish Journal of Medical Science*, October 1956, p. 427) reports that the operation was 'uniformly successful' in all 15 cases of spherocytic anæmia in which it was performed. In the one case of atypical congenital hæmolytic anæmia without spherocytosis in the series, there was little improvement following splenectomy. In six out of seven cases of idiopathic thrombocytopenia, splenectomy was immediately followed by cessation of clinical bleeding, and this beneficial effect has been maintained for periods ranging from two months to three years. The two cases of primary hypersplenism had a complete clinical and hæmatological remission, and the one case of Felty's syndrome (arthritis, splenomegaly and leucopenia) was improved by splenectomy. In the one case of myelosclerosis, splenectomy resulted in a permanent improvement in the hæmoglobin level, but operation was followed by hepatomegaly, apparently due to the liver taking over the functions of the spleen, and the pathological changes in the bony skeleton continued to progress, accompanied by severe and often crippling bony pain. Splenectomy failed to benefit two cases of primary aplastic anæmia with normal bone marrow, one early atypical case of chronic myeloid leukæmia, and one case of lupus erythematosus presenting as apparent idiopathic thrombocytopenic purpura.

A new Medicine Measure

To anticipate the more general use of the metric system in prescribing, which is expected from the recommendation to discontinue the use of the apothecaries' system in the 1958 *British Pharmacopœia*, H. J. Benzies and J. E. Cocking,

of the Sheffield United Hospitals, have devised a medicine measure graduated in both the metric and the imperial system (*Pharmaceutical Journal*, November 17, 1956, **177**, 395). As can be seen in the accompanying illustration, the metric side is graduated at 4, 8, 15, 30, and 60 millilitres, these being the usual doses required when a mixture is prescribed in this system. This measure is now being used exclusively in the wards and departments of the United Sheffield Hospitals. The authors conclude their short note as follows: 'It is a matter for conjecture how long it will be before patients themselves will be able to measure out their medicines in millilitres, but this idea may not be as Utopian as it sounds'.

REVIEWS OF BOOKS

Operative Surgery, Vol. I and II. EDITED BY CHARLES ROB, *M.C.*, M.CHIR., F.R.C.S., and RODNEY SMITH, M.S., F.R.C.S. London: Butterworth & Co. (Publishers) Ltd., 1956. Pp. xl and 750. Illustrated. Price £5 10*s.* per volume.

A NEW book on operative surgery by Charles Rob and Rodney Smith is quite an event. The authors are young, and know what surgeons want. They are 'Surgical Travellers', and they know what surgeons are doing. They are eminent enough and tough enough to scrap without compunction the obsolete stuff that fills most textbooks. They start with two principles: to describe the operations in pictures, the text being merely auxiliary, and to choose authors with particular experience. The idea is good. It does not quite come off.

'A book of all the Talents' tends to be, like a Command Variety Performance, a jumble without real cohesion. The choice of authors has been made with the emphasis on youth, and some of them have not yet cut their wisdom teeth. They write well, but they have bitten off more than they can chew. Cholecyst-gastrostomy and Longmire's operation have been tried, found wanting, and abandoned. The publication of the operation described on page 312, volume II, without an apology to Heath Robinson, suggests surgical immaturity.

It is, however, the basic thesis of the authors that 'if the best way to learn operative surgery is to watch an operation perfectly performed, the emphasis in a book on operative surgery must be visual', that has proved wrong. Illustrations can never show an operation; they can only explain, in a highly conventionalized form, matters described in the text. The illustrations in this work show all the skill and all the limitations of the professional artist, and they follow the accepted (indeed, the necessary) conventions. Normal anatomy is distorted to show things that cannot really be seen. The stomach is an inflated balloon, the omentum a semi-transparent sheet of muslin through which a segmentally constricted tube is clearly visible, blood is a string of black beads, an ulcer is a rosebud on a flat surface, and an anastomosis is done with twenty stitches to the inch. Such illustrations can teach something if they are labelled, and if they are referred to in the text. The editors, having assumed that a string of pictures can tell their own story, have allowed no titles, no lettering, no captions to say what each figure is about. The authors, meanwhile, chat away in tiny paragraphs that have no direct reference to the figure next door: paragraphs that have been so condensed to fit the idea that the pictures have already told the story, that they are not really helpful. The effect is that of a not very good film without titles, accompanied by a running commentary from a speaker who is not looking at the screen.

There is a lot of good stuff in these volumes, but it needs a lot of experience to be able to use it.

Treatment of Migraine. BY JOHN R. GRAHAM, M.D. Boston, Massachusetts: Little, Brown & Co.; London: J. & A. Churchill Ltd., 1956. Pp. vii and 149. Figures 8. Price 28*s.*

THIS latest addition to the *New England Journal of Medicine* Medical Progress Series is written by the director of the headache clinic of the Massachusetts General Hospital. It is a refreshingly sane and practical approach to a subject which has lent itself to more uncritical therapeutic enthusiasm than any other in the whole field of medicine. Accepting as a working basis the concept that the migraine patient 'has inherited a neuro-physiological system . . . that for reasons as yet unknown is peculiarly susceptible to the deleterious effects of a variety of stresses', and that in many cases the patient 'is also endowed with a personality that in itself promotes the occurrence of stress', Dr. Graham stresses the importance of treating the patient rather than the disease. His great standby for the acute phase are the ergot alkaloids, the use of which he describes in detail.

This is the most valuable practical book on the subject which has yet been published. The only criticism is of the price: 28 shillings is a lot of money to pay for 122 ($7\frac{1}{2}$ x $4\frac{1}{2}$ inch) pages of text, 16 of references and 11 of index.

Subarachnoid Hæmorrhage. BY JOHN N. WALTON, M.D., M.R.C.P. Edinburgh: E. & S. Livingstone Ltd., 1956. Pp. xv and 350. Figures 25. Price 30*s.*

So much of the recent work on subarachnoid hæmorrhage has stemmed from surgeons that it is timely and fitting that the subject should be reviewed by a physician. Dr. Walton's book is based upon a thorough review of over 700 references, and an analysis of the case-records of 316 examples of subarachnoid hæmorrhage admitted to the Royal Victoria Hospital, Newcastle, from 1940 to 1949. Of these patients, 30 were seen personally during the acute illness and 106 were examined later. In addition there is an interesting analysis of the pathological findings in 82 of the 140 fatal cases in the series.

Although little that is new results from this labour, Dr. Walton is able to confirm most of the current beliefs. He emphasizes some of the rarer but still important causes of subarachnoid hæmorrhage, gives a detailed account of its symptoms, signs and differential diagnosis and finishes with a judicious survey of modern tendencies in diagnosis and treatment.

This book is well printed, clearly illustrated and reasonably priced. It can be confidently recommended as a source book to all those concerned in the management of this distressing disease.

An Outline of Bacteriology and Immunity. By RONALD HARE, M.D. London: Longmans, Green & Co. Ltd., 1956. Pp. ix and 418. Illustrated. Price 35*s*.

IT is a pleasure to welcome a new, moderately priced textbook of bacteriology and to find that viruses and the concepts of chemotherapy are built into the structure and not merely added as two hasty chapters to the new edition. This book is founded on the lectures given by the author to the medical students of St. Thomas's Hospital. The academic approach is greatly enriched by the author's experience of hospital bacteriology and epidemiological research. The student will be grateful for the crisp and lucid presentation of facts, for some superb illustrations collected from individual experts and for many graphs and charts carefully collected from their original sources. The more important statements are given references at the foot of each page. Much attention is devoted to the importance of endemic and epidemic infection and there is a full and separate discussion on the sources and modes of spread of micro-organisms. Immunity processes are treated less enthusiastically. It is a pity that more attention was not spared for the cellular aspects of immunity. Thus, the formation of antibodies is vaguely referred to the reticulo-endothelial system, and the plasma cell has no mention. The student may find difficulty in comprehending some disease processes, such as tuberculosis, for the various aspects of pathogenesis often are not integrated.

Nevertheless here is an excellent book, thoughtfully written, carefully checked, and elegantly produced.

The Lung as a Mirror of Systemic Disease. By ELI H. RUBIN, M.D. Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications, 1956. Pp. xx and 288. Figures 92. Price 95*s*.

CHEST specialists may well claim that their territory is so often invaded by pathology of every kind that they are, or should be, the least specialized of specialists. This book reflects this claim as it sets out to describe the ways in which the lungs are affected in diseases that are primarily non-pulmonary or generalized. It succeeds in this object and provides a useful and up-to-date summary and guide to the American and British literature on pulmonary lesions in metabolic, hæmatological, allergic, neoplastic, cardiovascular and 'collagen' diseases. Well-illustrated case histories are given of many examples from the author's experience. The absence of any special reference to the effects of generalized infections on the lungs is a curious omission. The book also discusses briefly the use of mass radiography in case finding and the clinical, radiological and pathological techniques which are used in the diagnosis of lung diseases. These sections are rather jejune for the physician likely to be interested in the rest of the book and are unessential for its main purpose. The production is excellent. This book should help both the general physician and the chest specialist confronted by an unusual case, to think of, and explore, general as well as local causes for pulmonary abnormalities.

Industrial Medicine and Hygiene. Vol. I-III. EDITED BY E. R. A. MEREWETHER, C.B., C.B.E., M.D., F.R.C.P., D.I.H., F.R.S.E. London: Butterworth & Co. (Publishers) Ltd., 1954, 1956. Pp. xxii and 1,494. Price £10 10*s* (£3 10*s*. per volume).

THE main purpose of 'the doctor in industry is to use medicine with other sciences to improve and preserve the highest standards of health in the individual and in the group'. The subject is therefore so wide that it touches on almost every branch of medicine and surgery, and many aspects of engineering and the law. It is difficult for a book on industrial medicine and hygiene to be comprehensive, but Dr. Merewether with his unique experience as a medical inspector of factories has collected the wisdom and experience of experts on many subjects such as factory legislation, the organization of industrial medical and nursing services, industrial pulmonary and skin disease, toxicology and rehabilitation. Generally these chapters are well written, but some are too long for the overburdened student and practitioner and others too erudite for any but the most expert. There are pearls of simple and informed writing on the medical aspects of compressed air illness, statistical and epidemiological methods, and medical services in inland transport.

The doctor who contemplates industrial medicine as a career or as a part-time occupation may be overwhelmed by the vast array of

subjects displayed. He may find it difficult to unravel from the various chapters on medical services what it is he has to do as a doctor in industry. Nevertheless, there is now available to him in these three volumes one of the most comprehensive and valuable sources of reference on industrial medicine in the English language.

The Morphology of Human Blood Cells. By L. W. DIGGS, M.D. Philadelphia and London: W. B. Saunders Co., 1956. Pp. xiii and 181. Figures 54. Price 84*s*.

THIS is essentially an atlas of blood cells supplemented by some 100 pages of descriptive matter, including a short chapter on technical methods. The illustrations include 30 coloured plates which, with the exception of one photomicrograph in colour, are reproductions of water-colour paintings. The remaining illustrations are mostly monochrome photomicrographs. The quality of the illustrations, both coloured and monochrome, is reasonably good on the whole, but a few are unsatisfactory. The plate of the erythrocyte series would be of little help, if not positively misleading, to anyone desiring guidance in the identification of megaloblasts.

In general, this book is probably no better and no worse than several other hæmatological atlases that have been published during recent years. A modern note is struck, however, by a chapter on the lupus erythematosus cell well illustrated in monochrome. Like all such atlases, it may serve a useful purpose for occasional reference, but for the beginner it is no substitute for adequate training and experience.

The Sexual, Marital and Family Relationships of the English Woman. By DR. EUSTACE CHESSER, in collaboration with JOAN MAIZELS, LEONARD JONES and BRIAN EMMET. London: Hutchinson's Medical Publications Ltd., 1956. Pp. xxxvi and 642. Price 75*s*.

THIS bulky volume, with its pretentious title, purports to present a survey of the social psychology of marriage and the family. It reproduces the method of statistical survey so fashionable in modern sociology and is based on questionnaires filled up by 6,800 women, selected 'at random' by 1,500 doctors.

The book consists of 479 statistical tables; these are difficult to follow and the graphs which accompany them are hardly more helpful. It is most unfortunate that the unique opportunity afforded by this survey and the valuable scientific information that it might have provided have been largely thrown away, since this large mass of so-called statistics cannot be considered reliable by even an amateur of the subject. It is admitted early in the book that the 'sample' is not a representative one. It is grossly biased towards the upper income groups of the Registrar General's classification. The statistical tables are based, not often on facts, but on subjective impressions. For example in many tables the woman was asked to state if her marriage was exceptionally happy, very happy, fairly happy, unhappy or very unhappy, a question to which the most intelligent woman might find it difficult to give an unqualified answer, and one to which the answer might vary according to the mood of the moment. The topics dealt with are in themselves of the greatest interest. They include childhood influences and sex education, religious influences, including a study of church attendance, single adult life, and married adult life including married happiness, birth control and sexual satisfaction.

Apart from the doubts felt about the statistical validity of this work, it nevertheless presents features of interest. The incidence of happy marriages in this series is high. The point is shown repeatedly that a happy and secure childhood and sensible sex education are important factors in the eventual achievement of marital happiness. It is a pity that all the effort expended in the production of this book was not allowed, on account of the invalidity of the statistical methods, to produce a social document of real value.

Physics, Psychology and Medicine. By J. H. WOODGER, D.Sc. Cambridge University Press, 1956. Pp. x and 145. Price 8*s*. 6*d*.

IN this fascinating essay, Professor Woodger pleads the cause of medical psychology and glances at many interesting problems. He warns against admitting phylogenetic hypotheses which lead to an artificial human standard of dominance—definitely non-U. Prejudices about 'mind' and 'matter' are still hard to overcome, although Russell has shown that the difficulties have their origin in bad metaphysics and bad ethics; a point in space-time may be a class of events and there is no reason why some of these should not be mental. In view of the wide implications of De Moivre's formula, it might have proved an intriguing illustration in the thesis.

This is an enjoyable essay, and at the end of it the reader can echo the Song of the Three Jovial Huntsmen—'We'm prowler't up and down a bit and had a rattling day'.

Women of Forty. By M. E. LANDAU, M.D., F.R.C.S. London: Faber & Faber Ltd., 1956. Pp. 49. Price 5*s*.

'LIFE begins at 40' is the theme of this useful little book written for the patient who has

reached the climacteric or menopause. It is written with simplicity and with very few technical terms. Mrs. Landau approaches the subject of the climacteric as a phase when discipline is required. For example, she makes it quite clear that obesity is usually quite unnecessary and that its control is of great importance in raising the morale of the patient passing through the discomforts of the menopause or the climacteric. She wisely advises no patient to 'put up' with even moderately severe flushes in this era of hormone therapy even if it does carry the occasional and annoying complication of œstrogen-withdrawal bleeding. The important question of irregular bleeding at the climacteric or post-menopausal bleeding is clearly stated as a possible symptom of serious uterine disease but the warning is gently given and should not produce cancerophobia or even undue introspection in the lay reader.

Since sympathetic explanation is the basis of any form of treatment of menopausal symptoms it is useful to be able to supplement one's words with a loan of a small and simple book, although at the price few patients will complain at having to buy a copy.

One Doctor in His Time. By BETHEL SOLOMONS, M.D., F.R.C.P.I., F.R.C.O.G., M.R.I.A. London: Christopher Johnson Publishers Ltd., 1956. Pp. 224. Illustrations 9. Price 18*s*.

'QUIDQUID agunt homines'. One is reminded of Juvenal's phrase on reading Dr. Solomons' book for indeed it recounts the varied pleasures of an active life, and is also concerned with the wishes, fears and joys of humanity as revealed to a gynæcologist of fame and experience. The author gives a straightforward account of his life which will be enjoyed by non-medical readers, doctors, or by students who had the fortune to pay a visit to the Rotunda in the days of his Mastership. He writes of Trinity College, Dublin, of international rugger, Irish personalities and Dublin life, American visits, professional gynæcology, and hunting. To quote Juvenal again, something of a 'farrago'.

Dr. Solomons has been fortunate in already having been granted length of life, let us hope in retirement he is further granted 'multos annos' to come.

NEW EDITIONS

The Queen Charlotte's Textbook of Obstetrics, in its ninth edition (J. & A. Churchill Ltd., 45*s*.), has graduated to the status of one of the old faithfuls of undergraduate teaching. Since its first edition in 1927 it has kept up a fairly steady average of a further edition every three or four years. New members of the hospital staff have clearly infused it with new ideas and, unlike many books which are the combined, or not so combined, work of a number of authors, it has almost the consistency of a single writer's work. This is probably because it sets out faithfully, and without argument, to describe the present practice of the famous institution whose name it bears. A great deal of really up-to-date information has been woven into the text and much deadwood has been cut away although there is still more to be got rid of, such as external pelvimetry and the assault upon the fœtal scalp with Willett's forceps at lower segment Cæsarean section (fig. 210). Destructive operations on the fœtus have perhaps still too much pride of place for the needs of most students, although it must be hard to dispense with the gruesomely excellent illustrations. Cæsarean myomectomy ought to be more roundly condemned and more might be made of the risks and complications of induction of labour, especially where labour does not ensue. These, however, are trivial criticisms of an edition which is likely to enjoy the popularity of its predecessors and certainly deserves it.

Emergencies in Medical Practice, edited by C. Allan Birch, M.D., F.R.C.P., in its fifth edition (E. & S. Livingstone Ltd. 37*s*. 6*d*.) is even better value for money than its predecessors—and that is saying a lot. The whole book has been revised, and several chapters have been completely rewritten. A book which requires a new edition every two years—as this one does—is obviously meeting a real demand, and it is not difficult to understand why Dr. Birch's book sells out so quickly. For those who already have it, further praise is unnecessary. To those who do not yet possess a copy all that need be said is that this is a book which no practitioner can afford to be without. It is as comprehensive as it is reliable and practical.

Diseases of the Heart, by C. K. Friedberg, M.D., in its second edition (W. B. Saunders Co., 126*s*.) has undergone thorough revision, particularly in the sections devoted to cardiac surgery. Three new chapters devoted to graphic methods of examination have been added. The teaching throughout is sound, and the book can be thoroughly recommended as a reliable textbook on the subject for the practising clinician. The doubling of the price, however, will militate against its ready purchase in non-dollar countries.

Bing's Local Diagnosis in Neurological Diseases, by Webb Haymaker, M.D., translated, revised

and enlarged from the fourteenth German edition (Henry Kimpton, £6 5s.).—Bing's Compendium of Regional Diagnosis first appeared in English some forty-five years ago, but it disappeared from circulation in the early inter-war years. The volume which now appears is very different from the old English version of the Compendium, and is evidently considerably modified from the latest German edition of Bing's classic, since it contains many references to the most up-to-date English and American literature. It can certainly be commended for its completeness; between its covers there is amassed an immense amount of neurological knowledge, and in addition to the work of the main editors there are two chapters on neuro-radiology by Dr. Bernard Epstein and a chapter on electroencephalography by Dr. R. G. Berry. The list of references to recent literature is imposing. The book really suffers from the inclusion of too much information, because, in not a few instances, the description of details and exceptions completely outweighs the description of the standard doctrine. This makes the book in some ways impractical; the details presented may be of great value to the neurologist, but will make the book very difficult reading for the student.

Whilst the effects of pouring a great deal of new wine into an old bottle cannot be altogether happy, the completeness of the book is a great merit.

A Course in Practical Therapeutics, by M. E. Rehfuss, M.D., F.A.C.P., and A. H. Price, M.D., in its third edition (Baillière, Tindall & Cox Ltd., 12os.) continues to subserve a useful function as a comprehensive and authoritative work of reference. It is largely a product of the Jefferson Medical College, Philadelphia, and epitomizes the sound teaching which characterizes the Philadelphia school of medicine. The placing of 'symptomatic therapy' before 'treatment of specific disorders' is to be deprecated, and the illustrations are not of the high standard which one expects in a book of this standing. These criticisms apart, however, the book can be recommended as a useful work of reference which should find a place in every medical school and hospital library.

The Dental Treatment of Maxillo-Facial Injuries, by Sir William Kelsey Fry, C.B.E., *M.C.*, M.D.S., F.R.C.S., F.D.S., and Terence Ward, M.B.E., F.D.S.R.C.S., second edition (Blackwell Scientific Publications, 47s. 6d.).—The first edition of this book was published in 1942 and shortly afterwards followed the supplement. This supplement was devoted to the description and treatment of the actual cases. It was a valuable addition and the second edition combines both books. Mr. Ward replaces three of the original authors. There are two new chapters. Sir Archibald McIndoe has contributed a chapter on middle-third fractures of the face; Mr. Kramer one on sulphonamide and antibiotic therapy. Both are valuable additions. Fractures in children are not considered; they would merit an additional chapter in future editions. The new edition is not substantially altered and the reader will find that, as before, this book is based on sound common sense. It is clearly written, the illustrations are good, and the price is reasonable. This book will remain a valuable textbook for those interested in this subject.

Textbook of Physiology and Biochemistry, by George H. Bell, M.D., B.SC., F.R.F.P.S.G., F.R.S.E., Norman J. Davidson, M.D., D.SC., F.R.F.P.S.G., F.R.I.C., F.R.S.E., and Harold Scarborough, M.B., PH.D., F.R.C.P.ED., M.R.C.P., in its third edition (E. & S. Livingstone Ltd., 60s.) shows every evidence of careful revision. There is, for example, a recognition of the additional factors involved in blood coagulation including the antihæmophilic globulin, and a somewhat fuller consideration of iron metabolism in relation to blood formation. The section on acidosis and alkalosis has been largely rewritten and transferred to a new chapter on the fluids of the body—a considerable improvement in the reviewer's estimation. The writing has not become quite impersonal; indeed the anatomical basis of skin sensation provokes the authors to moralize on 'excessive preoccupation with the outmoded notion that function is always necessarily dependent upon specific structure'. Having regard to continuous advances in physiology and biochemistry the authors' apology for having added nearly 100 pages to the first edition can readily be accepted. As a general textbook for all students it can certainly be recommended and its popularity is bound to increase.

BINDING CASES

Binding cases for this and previous volumes are available in green cloth with gilt lettering, price 5s. 6d. each post free. The cases are made to hold 6 copies after the advertisement pages have been removed; they are not self-binding. Alternatively, subscribers' copies can be bound at an inclusive charge of 13s. 6d. per volume; this includes the cost of binding case and return postage.

The contents of the February issue, which will contain a symposium on 'Diseases of the Blood' will be found on page A108 at the end of the advertisement section.

Notes and Preparations see page 137.

Fifty Years Ago see page 141.

Motoring Notes see page A91.

Travel Notes see page A97.

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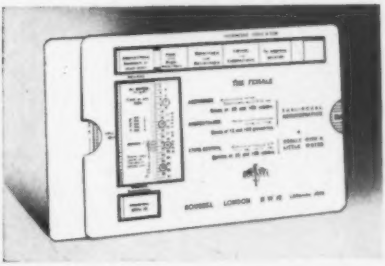

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NOTES AND PREPARATIONS

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'PIPTAL' (*N*-ethyl-3-piperidyl-benzilate methobromide) is intended for the treatment of 'peptic ulcer and other disorders of the stomach, duodenum and lower œsophagus'. It is said to 'give rise to fewer side-effects than any known anticholinergic', but its use is contraindicated in cases of glaucoma. Available as dry-coated, 5-mg. tablets in bottles of 50 and 500. (Benger Laboratories Ltd., Holmes Chapel, Cheshire.)

'POLYBACTRIN' antibiotic powder spray contains neomycin sulphate, 750 mg.; polymixin B sulphate, 150,000 units; zinc bacitracin, 37,500 units; and propellent, 83.5 g. It is intended for use 'on any broken tissue surface as a prophylactic or treatment' and 'there are no contraindications'. It is stated that 'a two or three second spray is sufficient to secure bacterial inhibition over a wide area'. The container is covered with a protective coating of polyvinyl chloride, and experimental breakage 'with considerable force demonstrated that the coating held all the splintered glass together'. (Calmic Ltd., Crewe Hall, Crewe.)

'ROMICIL' capsules contain a new antibiotic, oleandomycin, isolated from a strain of *Streptomyces antibioticus*, which is water-soluble and stable within a pH range of 1.1 to 9, 'thus ensuring good absorption and eliminating the need for enteric coating'. The capsules are 'relatively non-toxic yet clinically effective by mouth' in the treatment of 'pneumococcal and streptococcal infections of the respiratory tract and middle ear, especially in patients known to have become sensitized to penicillin', and also in 'staphylococcal infections, including osteomyelitis, especially those due to strains which are penicillin-resistant'. Available in strengths of 100 mg. and 250 mg., in packs of 12 and 100. (Roche Products Ltd., 15 Manchester Square, London, W.1.)

'SEA PEARLS' are fish-liver-oil capsules which each contain 4,500 I.U. of vitamin A and 450 I.U. of vitamin D. They are said to be especially suitable for children 'because they are so small', and the dosage is one capsule a day. Supplied in metal dispenser packs of 100 capsules, which release one capsule at a time. (Mayborn Products Ltd., Dylon Works, Berryman's Lane, Sydenham, London, S.E.26.)

'SOFRAMYCIN' skin ointment contains 1.5% of soframycin, an antibiotic isolated from *Streptomyces decaris*, and is said to be 'outstanding' in its activity against staphylococci, *Proteus vulgaris* and *Ps. pyocyanea*. It is 'extremely stable' and 'very soluble in water, which facilitates local treatment of infected skin and wounds'. It is 'not inactivated by blood, pus or serum'. Available in tubes containing 15 g. (Roussel Laboratories Ltd., 847 Harrow Road, London, N.W.10.)

'STERISIL' vaginal gel is said to be 'effective in the treatment and management of vaginal and cervical infections caused by *Trichomonas*, *Monilia*, *Hæmophilus vaginalis* and mixed micro-organisms'. It contains 0.1% of *bis*-1, 3-beta-ethylhexyl-5-methyl-5-aminohexahydropyrimidine (hexetidine), which is said to have 'an unusually strong affinity for tissue without loss of bactericidal action'. It is 'odourless, non-staining and non-toxic' and is available in tubes containing 1½ ounces (42.5 g.) with six disposable applicators. (William R. Warner & Co. Ltd., Power Road, London, W.4.)

NEW APPARATUS

A NYLON KIDNEY BASIN which is 'lightweight, unbreakable, free from clatter in use and which is sterilizable by boiling and cools quickly' has been added to the 'bex' range of housewares manufactured by the Halex Division of the British Xylonite Co. Ltd. Available in green or natural colour, in sizes of 8 and 10 inches. (Highams Park, London, E.4.)

PHILIPS X-RAY STYLO-THERAPY APPARATUS operates in the grenz-ray range of 5-25 kV. and at 'very short target-skin distances'. The apparatus is 'extremely compact' and portable and the manufacturers state that 'whilst it is ex-

pected that its main use will be in the treatment of eye conditions, the minute x-ray tube and shield—not much larger than a standard cigarette—opens up new possibilities for the x-ray treatment of hitherto inaccessible parts of the body'. (Medical X-ray Division, Philips Electrical Ltd., Century House, Shaftesbury Avenue, London, W.C.2.)

BUTTERWORTH GOLD MEDAL

THE BUTTERWORTH GOLD MEDAL is awarded annually for an essay by a member or associate of the College of General Practitioners on a subject connected with general practice. The subject for this year's essay is 'The Science and Art of Prognosis in General Practice'. Essays, identified by motto only (with the author's name and address in a sealed envelope) and not exceeding 10,000 words, should be submitted to the Chairman of the Awards Committee, College of General Practitioners, 14 Black Friars Lane, London, E.C.4., not later than September 16, 1957.

BENGER PRIZES

BENGER LABORATORIES LTD. announce the establishment of the 'Benger Prizes for Original Observations in General Practice'. These prizes will be awarded annually, and will consist in the first year of three prizes of £250, £150, and £100, respectively. The prizes, which are open to medical practitioners actively engaged in general practice anywhere in the world, will be awarded for the best report on 'An original observation in general practice'. Entries, which must be received by July 31, 1957, should be sent to The Chairman of the Awards Committee, The College of General Practitioners, 54 Sloane Street, London, S.W.1, from whom full details can be obtained. The entries will be judged by the Awards Committee of the College of General Practitioners.

INVALID CHILDREN'S AID ASSOCIATION

THE many activities of the Invalid Children's Aid Association are admirably reviewed in the Association's annual report for 1955-56. During the year one more school and one more home were opened. The school is Pilgrim's School, Seaford, which is for boys with chronic ill health. Most of these are asthmatics or boys in whom allergy, emotional disturbance or possibly unsuitable management are playing a large part in making day-school attendance at home irregular and unsatisfactory. The new home is the Edith Edwards Home at Beaconsfield, which is for the care of healthy children exposed to tuberculosis infection in their own homes. The other homes and schools run by the Association include the Meath School, Otteshaw, for boys and girls, aged 3 to 10 years, suffering from bronchiectasis; the John Horniman School at Worthing, which provides temporary care for 24 boys and girls, between the ages of 7 and 16, who suffer from some physical disability; St. Michael's Home, Southbourne, which caters for 12 girls between the ages of 7 and 12, who are more in need of an atmosphere of security and affection than of convalescent home care.

A REPORT ON NURSING

IN June 1955, the Dan Mason Nursing Research Committee of the National Florence Nightingale Memorial Committee sent a questionnaire to over 1,200 nurses, male and female, who had passed their final examinations in 1953. Replies were received from 76.6% of these nurses, and an analysis of these shows that 20% of the female nurses had left nursing because of marriage, while 10% of the single nurses were planning to marry. The desire to work overseas accounted for the next largest loss: 4% were already overseas and a further 13% were planning to go. Of the single staff nurses, 37% intended to continue hospital nursing, but 24% of this group planned to nurse overseas and 14.5% were going to marry. More than one-third of the married nurses were nursing, mostly in hospital practice. The majority of the nurses, male and female, engaged in hospital nursing were non-resident. The criticisms of the present system of nursing included the hours of duty for hospital nurses, the status of the staff nurse, and the need for improved staff relationships.

Copies of this report, 'The Work of Recently Qualified Nurses', can be obtained from the National Florence Nightingale Memorial Committee, 7 Grosvenor Crescent, London, S.W.1. Price 2*s.* 6*d.*

SMOKING AND CANCER OF THE LUNG

IN a statement on the current controversy as to the cause of cancer of the lung, the council of the National Association for the Prevention of Tuberculosis expresses the opinion that 'those who smoke heavily should cut down their smoking. Cigarette smoking indeed is a habit better not started. It is worth while discouraging young people from ever smoking that first cigarette. Those who live in towns can support the campaign to reduce atmospheric pollution from smoke and fumes—both in industry and in homes. . . . By supporting mass radiography campaigns, and encouraging friends and neighbours to have a chest x-ray, we can help to discover the disease early and treat it successfully'.

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PUBLIC HOUSE HYGIENE IN GLASGOW

In a survey of 50 public houses in Glasgow, T. S. Wilson and H. S. Carter (*Med. Offr.* 1956, **96**, 257) found that only 18 beer glasses out of 142 satisfied 'the lenient U.S. Public Health Service standard' of not more than 100 organisms on the area swabbed. Fæcal *E. coli* were rarely found, but coliforms and mouth cocci were often isolated from 'clean' glasses. Of 93 whisky glasses examined, 34 yielded counts of less than 100 organisms on the area swabbed. Only 14 out of 27 bartenders' towels yielded bacterial counts of fewer than 500 per square inch, and only 14 out of 45 samples of wash water yielded a count of less than 500 per ml. Sanitary arrangements for customers were often unsatisfactory, and in 26 bars no separate washing facilities were available for the staff. It is reported that 'there was far too little hot water available in these public houses'. Overflow beer was found to be contaminated in the catchment tray, and it is recommended that 'spilled beer should not be allowed to accumulate in trays all day, as is common practice, and then passed back into the barrel, whether passed through a sieve or not'.

PÆDIATRIC OBITER DICTA

'Two things irritate me at clinical examinations, the medicated cotton-wool fleeces pinned by grandmothers beneath children's vests, and the unhygienic rigid garments known as liberty bodices, which appear even on schoolboys, the rationale of which must surely have gone out with schoolgirls' long stockings. Mothers never know why they buy these objects instead of simple free-stretching vests'.

'In my own family I am accustomed to nightmares, restlessness and occasional shouting in dreams, so that I deplore the unnatural worry parents display when these things happen to their children. Even sleep-walking, in moderation, is not a matter of serious disquiet. These are the price to pay for the enjoyment of television thrillers. All too often it turns out that in these homes the bedroom light, or at least the landing light, remains on throughout the night, and parents are tricked into spending hours lying down beside the children'.—Dr. C. C. Harvey, pædiatrician to the County Council of the West Riding of Yorkshire, in the annual report for 1955 of the County Medical Officer and Principal School Medical Officer.

SCHOOLCHILDREN'S FEET

In a survey of 1,400 schoolchildren, 468 (33.4%) were found to have foot defects, according to the annual report of Dr. I. Gordon, the medical officer of health for Ilford. Girls had a higher incidence of defects such as deflected terminal phalanx of the great toes than boys: 14% of all defects, compared with 9% among boys. There was also a higher incidence of hallux valgus among girls than boys: 34% of all defects, compared with 12% for boys. More girls had curled toes—presumably due to the wearing of tight shoes. The incidence of flat feet was equal in the two sexes, but the number of boys with valgus ankle was double that of girls. None of the children complained of pain in the feet or legs. The incidence of badly worn or unsatisfactory footwear was very low (0.2%), whilst 1.9% had dirty feet and dirty socks.

ADOLESCENT VENEREAL DISEASE

A report by T. Rosenthal and J. E. Vandow (*N. Y. St. J. Med.*, 1956, **56**, 3154) shows that in New York City there has been a statistically significant increase of 55% in the proportion of males in the 15-19-year age-group who acquired primary syphilis in 1954 as compared with 1940. In the same period the proportion of females acquiring gonorrhœa was more than doubled in this age-group in the same period—rising from 8.8% to 18.6% of reported cases.

FRENCH MORTALITY STATISTICS

In 1955, alcohol was responsible for 18,000 deaths in France—4000 more than the number of deaths from tuberculosis. There were 70,000 deaths from cancer, 8000 from road accidents, and 7000 from suicides.

ONE HUNDRED MILLION POUNDS OF ASPIRIN

The Monsanto Chemical Company, the manufacturers of aspirin, has just produced its 100,000,000th lb. (45 million kg.) of aspirin. This is equivalent to 115,000 million tablets of aspirin. The annual consumption of aspirin in the United States is now about 16 million lb. (7¼ million kg.), compared with 4 million lb. (1.8 million kg.) in 1935. This means that the consumption of aspirin in the United States has been increasing about twice as rapidly as the population growth.

MEDICAL PUBLISHERS' CATALOGUES

A browse through the catalogues of five of the medical publishing companies, which have recently been issued, indicates the wealth of first-class textbooks and monographs which are now available to the profession. Copies of these catalogues may be obtained on application to the publishers: Blackwell Scientific Publications, 24-25 Broad Street, Oxford. Cassell & Co. Ltd., 37-38 St. Andrew's Hill, London, E.C.4. Lloyd-Luke (Medical Books) Ltd., 49 Newman Street, London, W.1. Pitman Medical Publish-

ing Co. Ltd., 45 New Oxford Street, London, W.C.1. John Wright & Sons Ltd., The Stonebridge Press, Bath Road, Bristol, 4.

PUBLICATIONS

Collected Papers of the Mayo Clinic and the Mayo Foundation, vol. 47, edited by Richard M. Hewitt, M.D., *et al.*, is yet another interesting collection of selected papers from the Mayo Clinic and Foundation, covering the period December 1954 to November 1955. There are 56 papers published in full, as well as a further 53 abridged papers, a number of selected abstracts and a very convenient list of title references. As in previous years, the papers have been wisely chosen to have a wide appeal to both general surgeons and physicians as well as to medical practitioners. There are interesting contributions on the advances in cardiac and cardiovascular surgery and some excellent surveys of gastric carcinoma and its complications. Contributions on the ductless glands include accounts of some more recent work with radioactive iodine in hyperthyroidism. (W. B. Saunders Co., price 87*s.* 6*d.*)

Stalag Doctor, by I. Schrire.—Dr. Schrire was taken prisoner at the time of Dunkirk and was not released until the end of the War. He was then in the notorious Colditz prison. In between he sampled many prisoner-of-war camps, from East Poland to Brunswick. In these reminiscences he recalls his experiences with a vivid, if at times too scathing, pen. The book will be read with interest, however, by his fellow-doctors for the light it throws on how men behave in captivity and how demoralizing an effect the Nazi regime could have upon the medical profession in Germany. (Allan Wingate, price 13*s.* 6*d.*)

My Story, by Mary Lambie, C.B.E., is the story of the distinguished New Zealand nurse who became Director of the Division of Nursing in the New Zealand Department of Health. The only criticism of the book is that there is so little of Miss Lambie herself, but her picture of the nursing services in New Zealand makes most interesting reading. Even in her accounts of her travels abroad she concentrates on the work in hand, but there are one or two delightful examples of pawky humour. There is, for instance, the delicious scene at the international nursing conference in Washington, in 1947: 'Never will I forget eight of the London matrons, the most dignified women in the world, doing a Lambeth Walk round the floor'. Equally pleasing is her description of the young woman who interviewed her in a broadcast 'question-and-answer' session in the United States: 'She was a most forthright young lady who had spent her war service playing table tennis with troops throughout the Pacific'! (N. M. Peryer Ltd., and Lloyd-Luke, price 30*s.*)

Bronchitis is an admirable little pamphlet for patients, describing in simple language the causes, treatment and prevention of bronchitis. (National Association for the Prevention of Tuberculosis, price 2*d.* each, or 12*s.* 6*d.* per 100.)

Research Survey 1956 is an interesting review of the present status of our knowledge of the etiology and treatment of peptic ulcer. The publishers stress that much relevant information on these points could be supplied by general practitioners, and they are planning an investigation into the subject by general practitioners. Further details of this investigation, and also copies of the 'Survey', can be obtained from The Research Department, Mining and Chemicals Products Ltd., 86 Strand, London, W.C.2.

The First Hundred Years is a short history of corticosteroid therapy since the days of Thomas Addison. Requests for copies should be addressed to The Public Relations Officer, Pfizer Ltd., Folkestone, Kent.

NEW ENGLAND JOURNAL OF MEDICINE

SPECIAL CONCESSION RATE FOR SUBSCRIBERS TO *THE PRACTITIONER*

AS ANNOUNCED in The Month (p. 3) arrangements have been made for subscribers to *The Practitioner* to receive the *New England Journal of Medicine* weekly at a reduced annual subscription. This will be $9.00 (£3 10*s.*), instead of the usual overseas subscription rate of $10.50.

Orders for the *New England Journal of Medicine*, accompanied by remittance, should be sent to: The Publisher, *The Practitioner*, 5 Bentinck Street, London, W.1.

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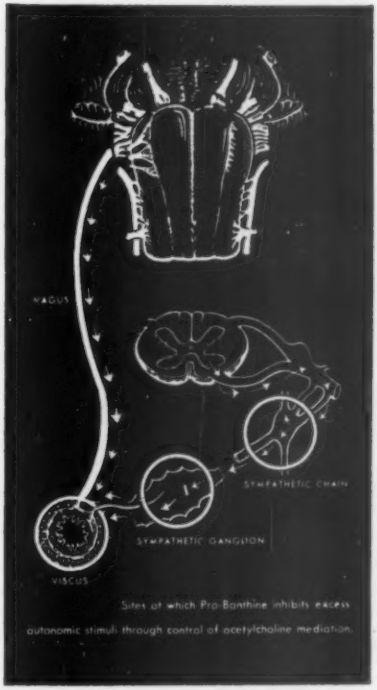

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[1]Gastroenterology (1953) 25 : 416.

[2]Gastroenterology (1953) 25 : 24.

SEARLE

PB : P96

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THE PRACTITIONER
Fifty Years Ago

'If Florence was in the grip of an epidemic of colds, coughs and fevers, astrologers were consulted, and they declared that it was caused by the influence of an unusual conjunction of planets. This sickness . . . came gradually to be known as "influenza".'—*The Chronicles of a Florentine Family*, 1200-1470.

JANUARY 1907

THE entire January number of *The Practitioner* fifty years ago is devoted to influenza and its complications. 'Abundant as have been our opportunities of studying influenza during the last sixteen years', writes the Editor, 'we have not yet learnt how to prevent its invasion, or how to stamp it out when it has got a footing in our midst . . . the names of the writers who deal with the various aspects of this "multi-faced" (if we may borrow the epithet which Southey applies to Satan) scourge are sufficient guarantees of the scientific value of their contributions'. The symposium is introduced in his usual elegant style by T. Clifford Allbutt, M.D., LL.D., F.R.C.P., F.R.S., Regius Professor of Physic, University of Cambridge: 'influenza is of protean diseases the most protean; more diversified even than syphilis, with which infection it shares, may I say even still, the elusive behaviour of its infectious element. In both, this element is caught, as it were, by glimpses, and its action so largely modified by incidental conditions, that, in the one as in the other, diagnosis is often a delicate balance of probabilities'.

What a galaxy of medical renown and of literary talent is found among the contributors! Sir Richard Douglas Powell, Bt, K.C.V.O., M.D., President of the Royal College of Physicians; Physician Extraordinary to the King, contributes 'A Note on Some Clinical Aspects of Influenza'. Sir William Broadbent, Bt, K.C.V.O., M.D., F.R.C.P., F.R.S., Physician in Ordinary to the King, deals briefly with 'The Therapeutics and Prophylaxis of Influenza by Quinine': 'In a large girls' school near London . . . the girls and mistresses took their morning dose but the servants were forgotten. The result was that scarcely any girl or mistress suffered, while the servants were all down with influenza'. Equally brief is Sir Dyce Duckworth, M.D., F.R.C.P., Consulting Physician to St Bartholomew's Hospital, on 'A Possible Source of Influenza'.

In his article 'Thoughts on Influenza', Sir John Moore, M.D., F.R.C.P.I., Professor of Medicine in the Royal College of Surgeons in Ireland, recalls that, when he was a boy, the term 'influenza' was used to describe an attack of acute catarrh of the respiratory mucous membranes from the nose to the bronchial tubes: 'It was, as it were, an echo of the great pandemic of influenza, which raged in the winter of 1847-1848. As years rolled by, the name fell more and more into disuse, until "influenza" at last became a mere tradition in medical nomenclature. And so things continued until the year 1889, when, with all the suddenness of a volcanic eruption, or of a devastating conflagration, the disease once more spread over the habitable globe . . . the historic pandemic was followed by

John Marshall Cowan, M.D., D.Sc., F.R.F.P.S.G. (1870-1947)

repeated "flarings" during the succeeding decade and a half, and, even to the present day, the tradition of the great outbreak finds expression in a diagnosis of influenza on very slender clinical grounds, and in a passionate fondness for the term on the part of a startled public'.

Samuel West, M.D., F.R.C.P., Physician to St. Bartholomew's Hospital, follows with 'Some General Considerations on Influenza'. Hector Mackenzie, M.D., F.R.C.P., of St. Thomas's and The Brompton, describes 'The Respiratory Complications of Influenza'; St Clair Thomson, M.D., F.R.C.P., F.R.C.S., of King's, deals with

'Influenza as it Affects the Nose and Throat'; Donald Armour, F.R.C.S., of the National Hospital, writes on 'Influenza and Appendicitis'.

John Cowan, M.D., D.Sc., of Glasgow, in his paper 'Cardiac Complications of Influenza' states that 'cardiac murmurs, of functional origin, are often found on examination of the heart after an attack of influenza. If no special symptoms are present, they are of little importance, but care must still be taken of the general health. Proposals for life assurance should, in consequence, always be postponed for some time after an attack, so as to prevent the annoyance caused by delay in acceptance'. John Marshall Cowan (1870-1947) came of a distinguished Glasgow medical family. Visiting physician to the Glasgow Royal Infirmary from 1907 to 1930, he helped to found the Cardiac Club, which became the British Cardiac Society, and he was one of the first to recognize the potentialities of electrocardiography. His book 'Diseases of the Heart', published in 1914, passed through three editions.

Wilfred Harris, M.D., F.R.C.P., Physician to the Hospital for Epilepsy and Paralysis, Maida Vale, discusses 'The Nervous System', T. Claye Shaw, M.D., F.R.C.P., of St. Bartholomew's, 'The Psychoses', H. Willoughby Lyle, M.D., F.R.C.S., Assistant-Surgeon, Royal Eye Hospital, Southwark, the 'Ocular Manifestations', and Arthur H. Cheatle, F.R.C.S., of King's, the 'Aural Complications'.

An interesting prophetic passage occurs in the paper 'The Micro-Organisms of Influenza' by W. D'Este Emery, M.D., Clinical Pathologist to King's College Hospital: 'The only possible solution that is entirely satisfactory is absolutely hypothetical and unsupported by any evidence. It is that influenza is a specific disease, due to a definite single cause, but that this cause is undiscovered, and perhaps unsuspected; or may be an "invisible" microbe . . . or some depressing "influence" acting directly on the human constitution, and of a nature as little known as were bacteria when influenza received its name'. A quarter-of-a-century had to elapse before influenza virus A was identified.

Arthur Newsholme, M.D., F.R.C.P., M.O.H. for Brighton, discusses 'Influenza from a Public Health Standpoint'.

The section 'By-Paths of Medical History' is devoted to 'Influenza in the Past'. 'Notes on Influenza from Foreign Journals' refer repeatedly to Leichtenstern of Cologne University, whose 'encyclopædic article' in Nothnagel's *Practice* 'still holds the field as an authoritative statement of the position of affairs, although written in 1898'.

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MOTORING NOTES

Plus Twenty Per Cent.

By ROBERT NEIL

UPPERMOST in most motorists' minds are the problems so recently raised by the resuscitation of petrol rationing. Although there is no doubt that practitioners will receive reasonable treatment from the authorities when they apply for a supplementary allowance, it is likely that even that allowance will be insufficient for the needs of many doctors with country rounds to do. Because of this all motorists, whatever their profession, are equally interested in obtaining the maximum possible mileage from each precious gallon of petrol. It is, perhaps, not generally realized what a surprising difference can be made to the fuel consumption of any car, merely by modifying one's normal driving style.

TIGHTER TYRES

Before considering driving styles, however, there are one or two points worth while checking on the car itself, so that the greatest possible benefit can be gained from improved driving. It is essential to check that when the brakes are in the 'off' position they are completely free, and that there is no sign of binding. Great care should be taken to prevent the tyres ever being run at a low pressure. If anything, it is worth while running the tyres at a slightly higher pressure than normal, as this will reduce rolling resistance to a great extent. Particularly as the start of petrol rationing coincides with wintry weather, it will be beneficial to have the wheel bearings cleaned out and greased with a slightly lighter grade of lubricant. This will help to reduce friction and therefore waste of petrol.

AVOID BRAKING

If endeavouring to drive in the correct style to save petrol the driver should regard use of the brake pedal as a crime. Every time the brake pedal has to be applied indicates that the throttle has been kept open too long. With experience drivers will find that, if they apply their attention well ahead, it will be possible to close the throttle and use the momentum of the car, letting the speed of the car diminish gradually as any obstruction is approached. This alone will save considerable petrol, but a larger saving can be achieved if the practice of coasting is used.

CULTIVATE COASTING

In spite of older theories on coasting this is perfectly safe, bearing in mind the efficiency of the brakes on a modern car, and can be effectively employed in both town driving and on the open road. On the average British main road it will be found that coasting can be employed for a large proportion of one's total mileage. Every time one approaches a stretch of slightly downhill road the gear lever should be slipped in to neutral; it will be found that a surprising distance will be covered before the speed drops so low that a gear should be re-engaged. Coasting should also be used whenever it is obvious, by looking well ahead, that it will be necessary to stop anyway. For example, if approaching traffic lights at red, a police controlled crossing, or a traffic jam of any type, it is clearly wasteful to keep the engine in use until the last moment, and then apply the brakes to dissipate the power which has been unnecessarily used.

By coasting whenever possible and safe, an increase of approximately 20% in the mileage covered on each gallon of petrol can be obtained. It should be stressed that there is no need to switch off the engine when coasting, as the amount of petrol used with the engine ticking over gently is minute. The least experienced of drivers need have no fear of coasting, as the efficiency of the synchromesh gearbox will allow top gear to be re-engaged whenever required, or, should circumstances change, for a lower gear to be engaged after coasting. Apart from coasting the petrol consumption can be lowered to some extent by driving much more carefully than one's normal style. Use of the lower gears should be reduced to the minimum possible, and top gear kept in use as long as the engine is pulling smoothly. In addition, if about 40 m.p.h. is regarded as a maximum speed further saving will be obtained. Even if obtaining supplementary coupons it is worth taking some trouble to obtain an increase of 20% in the miles covered against each coupon.

Although there are many cars which will run smoothly, and without pinking, on the lower and cheaper grades of fuel the position under rationing is not so much a case of saving money, as of spinning out the actual petrol. For that reason, on cars which will only just run satisfactorily on lower grade petrol, it might be advantageous to change to the more expensive grade. This might help to give a few extra miles per gallon, even if at slightly higher cost per mile.

LAYING UP THE CAR

A query from a reader regarding laying up his car, plus the fact that some readers who own more than one car and are affected seriously by rationing may be considering the same subject, suggests that a description of how it should be done might be of general interest. First the car should be carefully washed and then wax-polished, making certain that no moisture is left in any hidden corner of the bodywork, and then the chromium-plated portions should be given a protective coating of petroleum jelly, or one of the proprietary fluids sold for this purpose. Previously the carpets should have been thoroughly beaten and cleaned, and the car interior treated with an anti-moth compound.

If the car is to be laid up for as long as three months the sparking plugs should be removed and some thin engine oil squirted in to each cylinder. After replacing the sparking plugs the engine should be turned one or two revolutions, to distribute the oil evenly over the cylinder walls—naturally without switching on the ignition. While the car is laid up the engine should be turned over by means of the starting handle about once a week, to keep everything free and the lubricant in circulation. Before laying up the car it will be wise to have the battery charged by the local service station, and, if stored in a cool dry place, it will then be ready for service when the car is again put on the road. To avoid the tyres remaining constantly in the one position the car should be jacked up with all four wheels off the ground; this should be done carefully with wooden blocks or firmly placed bricks. The ordinary car jack can, of course, be used to raise the car initially. Before putting the car back into service it should be well greased, great care being taken to see that all old and solidified grease is forced completely out of each bearing.

When first starting the engine after the car has been laid up it is worth while removing the air cleaner and, once the engine is running evenly at a fast tickover, squirting thin engine oil in to the air intake. Too much should not be used, otherwise the engine may stall but a slight trickle for a few moments will help to lubricate the valves and the upper portions of the cylinder bores.

ADVANCED DRIVERS

There has been much talk, and discussion in the Press, on the recently formed Institute of Advanced Motorists, and the view has been expressed that any new motorist, who had only recently passed the 'L' test could, after a little instruction from an expert, pass in to the ranks of advanced motorists. This is I think a complete misunderstanding of the situation. I have studied the test with some care, and have satisfied myself that no-one other than a fully experienced driver whose skill has become almost instinctive could hope to succeed. In my opinion, this is as it should be. It is, I am afraid true that too many drivers relax their efforts once they have passed the compulsory test, during which they have done their best. The test for advanced motorists, if seriously taken, should help to give drivers an incentive to do their best, and if only enough motorists would at least attempt the tests laid down by the Institute the standard of driving would eventually be raised.

A group of overseas traffic officials at Hendon Police College, watching a demonstration of skidding by two police cars on the famous 'skidpan'.

The value of advanced driving instruction can easily be proved by examining the record of the school run at Hendon by the Metropolitan Police. During 1954—the last year for which complete records are available—there was one accident with a Metropolitan Police car in 72,587 miles, as compared with one in every 25,000 during 1939, and one in every 9000 miles in 1935. There can be little doubt that if all motorists drove in the habitual style of police drivers, or in the style of a successful examinee when passing the Institute's test, accidents would be considerably reduced. There are, no doubt, many drivers who consider themselves advanced motorists, but in some cases which I know of—and I am sure that my experience is not unique—the driver is distinguished by his flashy driving and efforts to show off. For the few individual drivers who are miserable when being driven, there are hundreds who pretend to be bad passengers, but the best sign of an advanced driver is that no passenger—himself a driver—could justifiably be worried by the driver's style and technique.

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'ROMILAR' is a true specific which may be prescribed for all types of useless cough.
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DOSAGE *Adults*: One to two teaspoonfuls (15 mg. to 30 mg.)
Children: Half to one teaspoonful (7·5 mg. to 15 mg.)
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These doses may be given one to four times daily.

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ETHNINE, a palatable and effective cough sedative containing pholcodine, is rapidly replacing preparations of codeine in the suppression of exhausting and harmful unproductive cough in children, adults and elderly patients.

The advantages of Ethnine are in its effectiveness with low toxicity, and its freedom from side-effects such as constipation and digestive upset.

For sedative cough therapy

ETHNINE

Trade Mark

Bottles of 4 and 80 fluid ounces containing 4 mg. pholcodine in each teaspoonful (4 c.c.)

PIRIEX, a carefully chosen combination of an improved antihistamine of low toxicity with expectorants, is unsurpassed in therapeutic activity where a stimulant expectorant linctus is indicated.

Piriex effectively liquefies tenacious sputum and aids its prompt removal. It is also an effective decongestant and is invaluable in the treatment of congestion of the upper respiratory tract.

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TRAVEL NOTES

Winter Holidays by Land and Sea

By PENELOPE TURING

WHEN I was a child my year was made up of two great festivals—Christmas and the summer holiday—and as soon as one was over I began to look forward to the other. Even when one is old enough to know that the brightest vision is not always realized, many of us still retain this thrill of holiday anticipation, which comes, as surely as the new calendar, with the beginning of another year. It does not really matter whether one's ideal is some Cornish cove or a pine-scented village in the Alps, Paris in May or the great silences of a Norwegian fjord. The sense of holiday is the main thing, release from the daily round, freedom from post or telephone bell, and the adventure of fresh sights and sounds or the comfort of familiar ones. Even frost-bound roads and burst pipes seem less intolerable when holiday plans are afoot.

SNOW OR SUN?

Where and when to go? Now that travel is so quick and easy there is virtually no limit on the places to which one can travel, even for a couple of weeks. When to go is a matter of personal taste or necessity, but it does of course affect the choice of place. There is a great deal to be said for winter or early spring holidays and it is still not too late to plan one, although it is advisable to take action about it without undue delay.

There are two main categories of winter holiday makers: the energetic who go forth to conquer with skis or skates in the snow and sunshine of the mountains, and the others who prefer their sunshine neat. Either way sun is one of the first essentials, and to be reasonably sure of finding it between January and April one must go abroad.

WINTER SPORTS

The attraction of winter sports is something apart, quite unlike other foreign holidays. The mountain scenery is a delightful background but its charms are really physical: the enjoyment of sheer exercise in wonderful air, the evenings of dancing or complete relaxation, and of course good food and drink. There is now an enormously wide choice of winter sports countries: Switzerland with its classic centres like St. Moritz and Davos, Austria, Italy, France, Germany and Norway. Regular enthusiasts will have their own favourites, but for the beginner it is a wise plan to go to one of the special centres which are run by the larger travel agencies, or to take one of the inclusive winter sports holidays which are available. In this way you are saved all trouble of planning, and can budget on a price which includes fares, accommodation, taxes, tipping, ski instruction, hire of skis, boots, sticks, and so on.

In general the higher the altitude the later the season continues; Zermatt (5,315 ft.) for example is a safe choice for the Easter school holidays, but is also one of the more expensive. Christmas and the second half of February are the most popular, and therefore costly, periods

FIG. 1. — View from the Wendelstein mountain, Bayrischzell.

almost everywhere so if cost is an important consideration it is wise to choose a holiday outside these times and in one of the less well-known places. For instance, the charming district of Bayrischzell (fig. 1) in the Bavarian Alps south of Munich, or a small centre in Switzerland or Austria.

There are, however, other points to be taken into consideration apart from relative prices. The larger and more popular centres are naturally better equipped with the 'mechanization' of winter sports such as ski lifts, and many have opportunities for the additional sports of skating and curling, ice hockey rinks, and so on. So in making the choice of where to go the facilities available for the kind of holiday you want must be balanced against price.

Again, there are those people who enjoy the setting of a mountain resort in winter without taking an active part in the actual sports. For a walking holiday the mountains are of course better in summer, but the important centres like St. Moritz or Garmisch offer plenty of opportunity for watching experts competing in special sporting events. Personally, for a non-ski-ing holiday (or for a ski-ing one too for that matter) I would choose the enchanting Bavarian village

of Oberammergau which is now one of Germany's well-known winter sports resorts. This is the home of the famous Passion Play, produced every ten years (due again in 1960) and one can spend fascinating hours there looking at the magnificent Passion Play Theatre, watching local wood carvers at work in the picturesque painted chalets, or exploring the bizarre beauty of Ludwig II's neighbouring castle of Linderhof.

SEEKING THE SUN

As a complete contrast there are voyages to warmer southern seas, which offer perhaps the most absolute relaxation to be found. Cruises are another specialized form of holiday which is either ideal or anathema to you. Most of the modern liners, and also the cargo ships which carry about a dozen passengers, are extremely comfortable and nowhere else, I think, do you get quite the same atmosphere of luxurious idleness. Dancing, bridge, deck games, swimming, even shops are all within your floating hotel if you want them, and so is a chair and a book in a quiet corner of the deck. The most exciting voyages are the longer ones to the Caribbean, South America or South Africa, but these take from six weeks to three months. For shorter trips the Canary Islands are a good winter choice, and one can have a 10 to 12 day voyage there and back on the Aznar Line ships which sail from London about once a fortnight until the middle of May. This of course gives only a brief glimpse of those fascinating islands

FIG. 2.—The coast line of Majorca.

where old Spanish grace is superimposed on the luxuriance of tropical flowers and vegetation. Alternatively, the Bergen Line *Venus* ships will take one to Madeira and the Canaries where you can spend ten days ashore, and the whole trip takes three weeks.

Sea voyages and winter sports have this in common, that one is in close proximity to fellow-men—often fellow-countrymen. If you want to get away from people, or to find the real atmosphere of a different land, then the only way is to strike out on an individual holiday. For this, in early spring, few places are lovelier than the Balearic Islands: Majorca, Minorca and Ibiza. In summer the influx of visitors is fast spoiling them, but March is an ideal time. Here one has the advantage of a rate of exchange which is in

FIG. 3.—Ibiza. The architecture is Moorish in influence. The stone is washed salt-white.

our favour: 109 pesetas to the £, excellent Spanish food, simple but adequate accommodation ranging to very good in the larger towns like Palma in Majorca, glorious scenery and fascinating old towns and villages.

Majorca, where the average day temperature in March is 62° F., is the largest and most popular, with a wonderful rocky coastline (fig. 2), a magnificent cathedral dating from the 13th century and unlimited scope for walking. The roads are not very good, nor are the bus and train services. Minorca is a dignified green island. On Ibiza, smallest of the three, the people still wear their traditional costumes as a matter of course, and the little town of Ibiza (fig. 3) itself has a history going back twenty-six centuries. Time has dealt gently with it, and until the demands of tourism submerge it much of the old peace remains.

COOKS (Berkeley St., London, W.1) have Swiss winter sports instruction centres at Kandersteg, Lenk and Engelberg and provide a 15-day holiday, including journeys, for three grades of skiers for 45-55 guineas. Festival Services Ltd. (32 Beauchamp Place, London, S.W.3) offer a 16-day inclusive holiday at Bayrischzell for 39½ guineas.

The Aznar Line 10 to 12 day voyage to the Canaries costs from £40; the three-weeks' holiday by *Venus*, including stay ashore, from £82.

B.E.A. has a direct flight to Palma, Majorca, which takes 3½ hours; return fare £43 13*s*., or £36 10*s*. by their mid-week off-peak rate. The alternate route by boat and train takes about 48 hours. First class return London-Palma £38 16*s*., second class £27 7*s*.

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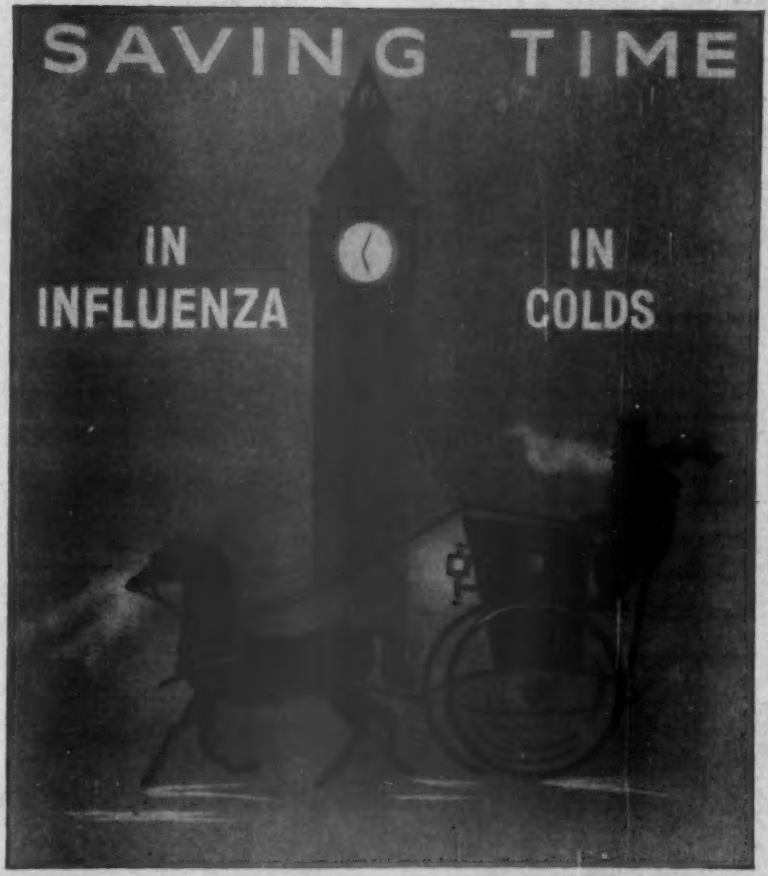

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